63rd Paediatric Pathology Society
Annual Scientific Meeting
7-9th September 2017
Lisbon, Portugal

**Venue:** VIP Executive Art’s Hotel

**Local organiser:** Paula Borralho Nunes
THURSDAY 7TH SEPTEMBER 2017

15.30 onwards: Registration

**17.00-19.00: Symposium on Fetal Hydrops**

_Chairs - Sophie Collardeau- Frachon and Paula Borralho Nunes_

Lecture – “Fetal Hydrops”
Eduardo Ruchelli, University of Pennsylvania, USA.

- **Inborn errors of metabolism revealed by fetal hydrops**
  Sophie Collardeau- Frachon, CHU de Lyon, France.

- **CHAOS syndrome**
  Sophie Patrier, CHU Rouen, France.

- **Fetal anaemia**
  Jelena Martinovic, Hopital Antoine Beclere, Clamart, France.

- **Next Generation Sequencing Panel**
  Soumeya Bekri, CHU Rouen, France.

_At the end of the session the attendees would be able to_

1. Acquire an insight on how to approach fetal hydrops
2. Know the main aetiologies of this condition
3. Know how to manage samples in order to make definitive diagnosis and prevent recurrence in siblings

_Followed by Welcome cocktail_
FRIDAY 8TH SEPTEMBER 2017

08:30-10:00:

Chairs – Samantha Holden and Marta Cohen

8.30-9.15 : Proffered papers

2 Oral presentations (10 mins speaking, 2 mins questions), abstracts pages 11-12:

O1 – 0830hrs – 0842hrs
“Decreased Production of Pro-inflammatory Cytokines: A Possible Mechanism of Lethal Infection in Infants”
Andrew R Bamber, Wendy Heywood, Kevin Mills, Neil J Sebire, UK

O2 – 0842hrs – 0854hrs
“Congenital plexiform cellular schwannoma: a "benign" but locally severely aggressive lesion
Ed Cheesman, A Kelsey, C Sethuraman, R Craigie, M Shah, B Brennan, R Santos, Manchester, UK

6 Poster presentations – each 3 mins speaking (with power point presentation), abstracts pages 13-18:

P1 - 0854hrs -0857hrs
“The intercalated disc in paediatric patients with dilated cardiomyopathy”
Elise L Kessler, Peter GJ Nikkels, Toon AB van Veen, University Medical Center Utrecht, The Netherlands

P2 – 0857hrs – 0900hrs
“Generalized Arterial Calcification of Infancy with compound heterozygous mutations in the ATP-binding cassette, subfamily C, member 6 gene and a review of the literature”
Kathrin Ludwig, Stefania Rizzo, Rudy Celeghin, Elisabetta Lazzarin, Marco Cason, Paolo Balli, Gaetano Thiene, Kalliopi Pilichou, Cristian Basso, Italy

P3 – 0900hrs – 0903hrs
“How does fetal brain/liver weight ratio vary by gestational age, degree of maceration and autopsy diagnosis?”
Bente Ediassen Opsjøn, Øyvind Salvesen, Christina Vogt, Department of Laboratory Medicine, Children’s and Women’s Health, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway
“Morphological variants of necrotizing enterocolitis of newborns”
Korchagina N.S., Nechaev L.V., Vorozhbieva T.E., Zhakota D.A., Tumanova E.L., Pirogov
Russian National Research Medical University, The N.F. Filatov Children's City Hospital, Moscow, Russia

“Inner ear and Sudden Infant Death: Exploring Implications for disturbances in brainstem functions”
Marta C Cohen, Trudy Donn, Marcelo Rivolta, Daniela Cacciabue- Rivolta, Elspeth Whitby, Daniel Rubens, Sheffield, UK

“Hippocampal anomalies of the dentate gyrus and sudden unexpected death in childhood”
Victoria A Bryant, Neil J Sebire, Thomas S Jacques, Great Ormond Street Hospital, UK

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**International Paediatric Pathology Association (IPPA) Graduates' slide seminar**

9.15 Dr Evelina Silvestri
9.30 Dr Gitta Turowski
9.45 Dr Diclehan Orhan

At the end of this session participants will
1. Acquire an insight into difficult and unexpected cases which may occur
2. Gain an approach to follow in unexpected cases
3. Gain further knowledge about unusual presentations which individuals may face

10:00-10.30 Coffee break

**10:30-12.00: ‘Meet the Expert’ session**

Chairs – Jo McPartland and Beata Hargitai

10.30 Luisa Santoro, University of Padua, Italy and Ronald de Krijger, Princes Maxima Centrum, Utrecht, Netherlands.

11.00 Ed Cheesman, Royal Manchester Children’s Hospital UK & Michael Ashworth, Great Ormond Street Hospital, London, UK.
11.30  Phil Cox, Birmingham Women’s Hospital, Birmingham, UK. “Understanding growth discordant monochorionic twins”.

Expected educational outcomes:
At the end of the session the attendees would be able to
1. Further enhance their knowledge of and approach to challenging complex cases
2. Gain further insight into technical aspects of these difficult cases
3. Have had the opportunity to review the material prior to the meeting and provide questions in advance which would assist in individual learning from cases

12:00-13:00: John Emery memorial lecture - Pierre Russo

Professor, Department of Pathology and Laboratory Medicine, Perelman School of Medicine at The University of Pennsylvania and Director of Anatomic Pathology at The Children’s Hospital of Philadelphia, USA.

Chair – Rita Alaggio

13:00-14:00: Lunch break

14:00-16:00: Proffered papers

Chairs - Gordan Vujanic and Alfons Nadal

8 Oral presentations (10 mins speaking, 2 mins questions), abstracts pages 19-27:

O3 – 1400hrs - 1412hrs
“Autopsy findings in concealed or denied pregnancy”
Sophie R Stenton and Marta C Cohen, Sheffield Children’s Hospital NHS FT, UK

O4 – 1412hrs – 1424hrs
“Necrotizing enterocolitis in twin pregnancies: relation with placenta anatomy”

O5 – 1424hrs – 1436hrs
“Limb body wall complex: definition and discussion of etiopathogenesis. A 8-year Tricenter Study “
Ana Costa Braga, Lucilia Monteiro, Paula Borralho Nunes, Marco Ferreira, Sophie Collardeau-Frachon, Hospital Professor Doutor Fernando Fonseca, EPE, Amadora, Portugal, Nova Medical School, Universidade Nova de Lisboa, Lisboa, Portugal, Centro Hospitalar Lisboa Ocidental, EPE, Lisboa, Portugal. Faculdade de Medicina da
Universidade de Lisboa, Lisboa, Portugal, Centre Hospitalier et Universitaire de Lyon - Hôpital Femme-Mère-Enfant, Lyon, France, Université Claude Bernard Lyon 1, Lyon, France

O6 – 1436hrs – 1448hrs
“Positive immunostaining for ATRX protein in neuroblastoma – does it exclude an ATRX gene mutation?”
Rose Chami, Anthony Arnoldo, Paula Marrano, Mary Shago, Paul Thorner, Hospital for Sick Children, Toronto, Ontario, Canada and University of Toronto, Ontario, Canada

O7 – 1448hrs – 1500hrs
“An analysis of the Relevant Condition at Death (ReCoDe) found in a series of Minimally Invasive Postmortems. How does it compare to the traditional Invasive Postmortem?”
Rachel Rummery, Jessica Agius De Giovanni, Ashok Raghavan, E Whitby, Marta C Cohen. Sheffield Children's Hospital, Western Bank, Sheffield, S10 2TH, United Kingdom.

O8 – 1500hrs – 1512hrs
“Taybi-Linden syndrome - Variability of the fetal phenotype”
Catherine Fallet-Bianco, F.Rypens, MA Delrue, M.Jovanovic, N.Patey, LL.Oligny, Canada

O9 – 1512hrs – 1524hrs
“Chorionic villi genotyping of fixed and paraffin-embedded tissues in molar and non-molar pregnancies”
Alfons Nadal, Carlota Rovira, Laura Magnano, Mireia Garcia, Elena Gonzalvo, Sandra Martinez and Marta Aymerich, Barcelona, Spain

O10– 1524hrs – 1536hrs
“Mitochondrial respiratory chain disease presenting as sudden unexplained death in infancy (SUDI) and Childhood (SUDC)”
Marta C Cohen, Olpin SE, Clark S, Hargreaves I, Poulton J, Taylor RW, Mortiboys H, Palmer L.
Sheffield Children’s Hospital, Sheffield, National Hospital for Neurology, Queen Square, London, John Radcliffe Hospital, Oxford; Wellcome Trust Centre for Mitochondrial Research, Newcastle. Great Ormond Street, London, UK

8 Poster presentations – each 3 mins speaking (with power point presentation), abstracts pages 27-34:

P7 – 1536hrs – 1539hrs
“Sudden Cardiac Death in Infancy and Childhood: findings from 20-years of autopsy”
Victoria A Bryant and Neil J Sebire, Great Ormond Street Hospital, London, UK
P8 – 1539hrs – 1542hrs
“High feto:placental ratio constitutes an independent risk factor for stillbirth”
*Ameila Heaford, C Mechler, E Karaa, Irene Scheimberg*, Royal London Hospital, Barts Health NHS Trust, London, UK.

P9 – 1542hrs – 1545hrs
“Mixed maturation patterns - when acceleration meets delay”
*Yvonne McCartney, Marie Culliton, Paul Downey, Eoghan E. Mooney*, Ireland.

P10 – 1545hrs – 1548hrs
“Microvillus inclusion disease: A clinicopathological study of three cases”
*Gucer S, Orhan D, Akçören Z, Talim B, Özen H, Temizel ?NS, Demir H, Kaymaz F, Aliefendio?lu D, Yüce A. Hacettepe University Faculty of Medicine, Ankara, Turkey*

P11 – 1548hrs – 1551hrs
“Preliminary Data on the Impact of Maternal Smoking During Pregnancy on Human Fetal Kidney Development”
*John S. Mulhern, Paul Brown, Natasha Walker, Michelle Bellingham, Heather M. Wilson, Moira Davie and Paul A. Fowler, Aberdeen, UK*

P12 – 1551hrs – 1554hrs
“Hyperechogenic bowel and congenital CMV infected foetuses”
*Liliana Gabrielli, Maria Paola Bonasoni, Giuliana Simonazzi, Donatella Santini, Claudia Pavia, Tiziana Lazzarotto*, St. Orsola-Malpighi University Hospital, Bologna, Italy, St. Maria Nuova Hospital, Reggio Emilia, Italy, St. Orsola-Malpighi University Hospital, Bologna, Italy, University of Bologna, Italy

P13 – 1554hrs – 1557hrs
“Development of a Novel Multiplex Post Mortem Test for Tissue Infection and Sepsis in Infants Using Tandem Mass Spectrometry”
*Andrew R Bamber, Wendy Heywood, Kevin Mills, Neil J Sebire, UK*

P14 – 1557hrs – 1600hrs
“Unusual fetal akinesia with caudal dysgenesis expanding the spectrum of MNX1 mutations”

16:00: PPS Annual General Meeting

18:00: Annual Gala Dinner
SATURDAY 9TH SEPTEMBER

09:00-10:30 Morning session

Chairs – Phil Cox and Peter Nikkels

09:00-10:00: Proffered papers

4 Oral presentations (10 mins speaking, 2 mins questions), abstracts pages 35-38:

O 11– 0900hrs - 0912hrs
“Macroscopic and Microscopic Placental Pathology in Stillbirths Versus Livebirths”
Amelia Heaford, C Mechler, E Karaa, Irene Scheimberg. Royal London Hospital, Barts Health NHS Trust, London, UK.

O12 – 0912hrs - 0924hrs
“Investigating sudden unexpected death in childhood: the results of a 20-year autopsy study”
Victoria Bryant and Neil J Sebire. Great Ormond Street Hospital, London

O13 – 0924hrs – 0936hrs
“Diagnostic Utility of Frozen Section in Paediatric Testicular and Paratesticular Lesions”
Srinivas Annavarapu, Corina Moldovan, Basil Bekdash, Hany Gabra. Royal Victoria Infirmary, Newcastle-upon-Tyne

O14 – 0936hrs – 0948hrs
“Placental findings and perinatal deaths: a national review using consensus terminology”
Yvonne McCartney, Edel Manning, Irene O’Farrell, Eoghan E. Mooney, Ireland

4 Poster presentations – each 3 mins speaking (with power point presentation), abstracts pages 39-42:

P15 – 0948hrs – 0951hrs
“Placental mesenchymal dysplasia: A case of clinical misdiagnosis and atypical p57 immunorexpression”
Sophie Stenton, L Pipe, Jens Stahlschmidt, Leeds, UK
“Causes of clinically unexplained stillbirths referred for full post mortem examination to a perinatal centre in the United Kingdom between 2009-2015”

**Marta Cohen, Cabrera MS, Zesic S, Blythe C, Zapata-Vazquez RE.** Sheffield Children’s Hospital NHS FT, Sheffield, UK and Facultad de Medicina, Universidad Autonoma de Yucatan Merida, Mexico

“Fine-needle aspiration cytology (FNAC) in children’s Mycobacterial lymphadenitides”

**Barbara Cafferata, Rita Alaggio, Patrizia Dall’Igna, Luisa Santoro, Guendalina Mognato, Fassina Ambrogio.** University of Padua, Padua (PD), Italy

“Prospective study of rapid diagnosis of acute funisitis in placentas from neonatal intensive care babies.”

**Virginia R Sams, W Fullerton, UK**

10:00 - 10:30: “I never expected to see this”

10.00  **Peter Bode**, University of Zurich, Switzerland.

10.15  **Beata Hargitai**, Birmingham Women’s Hospital, Birmingham, UK.

At the end of this session participants will
1. Acquire an insight into difficult and unexpected cases which may occur
2. Gain an approach to follow in unexpected cases
3. Gain further knowledge about unusual presentations which individuals may face

10:30-11:00: Coffee

11:00-13:00: Slide seminar on Gastrointestinal and Liver Pathology

*Chairs – Nicky Graf and Suzanne Mol*

11.00  **Metabolic liver disease** – **Pierre Russo**, University of Pennsylvania, USA

11.30  **Non-alcoholic fatty liver disease** – **Paula Borralho Nunes**, Hospital Cuf Descobertas, Lisbon, Portugal

12.00  **Liver tumours** – **Nicole Graf**, The Children’s Hospital at Westmead, Sydney, Australia

12.30  **Gastrointestinal polyps** – **Fatima Carneiro**, Medical Faculty of Porto, Portugal
Expected learning outcomes:
1. Understand an approach to the pathological diagnosis of liver tumours children, including description of the histological features and differential diagnosis of the major tumour types.
2. Understand the approach and diagnosis of non-tumour liver pathology with respect to metabolic and non-alcoholic liver disease
3. Update on diagnosis of gastrointestinal polyps in children

13:00 Close

The 63rd Annual Meeting of the Paediatric Pathology Society, Lisbon, Portugal, 07/09/2017- 09/09/2017 has been accredited by the European Accreditation Council for Continuing Medical Education (EACCME®) with 12 European CME credits (ECMEC®s). Each medical specialist should claim only those hours of credit that he/she actually spent in the educational activity.

Through an agreement between the Union Européenne des Médecins Spécialistes and the American Medical Association, physicians may convert EACCME® credits to an equivalent number of *AMA PRA Category 1 Credits*™. Information on the process to convert EACCME® credit to AMA credit can be found at [www.ama-assn.org/go/internationalcme](http://www.ama-assn.org/go/internationalcme).

Live educational activities, occurring outside of Canada, recognised by the UEMS-EACCME® for ECMEC®s are deemed to be Accredited Group Learning Activities (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada.

We hope you have had an educational and enjoyable experience at this year’s meeting.

Please complete your feedback forms.

**PPS President** Rita Alaggio  
**Local organiser:** Paula Borralho Nunes  
**Programme organisers:**  
**Secretary** Samantha Holden  
**Educational Sub-committee** Sophie Collardeau- Frachon
Nicole Graf
Jo McPartland
Abstracts

Friday 8th September Morning Session

O1

Title:

Decreased Production of Pro-inflammatory Cytokines: A Possible Mechanism of Lethal Infection in Infants.

Authors:
Andrew R Bamber, Wendy Heywood, Kevin Mills, Neil J Sebire

Background:

Hypothesis:

Aims:

Infection is the most common cause of explained Sudden Unexpected Death in Infancy. It is not clear why some infants succumb to infection in the community with few apparent preceding signs of severe illness. This study aimed to investigate the inflammatory response in these patients.

Materials and Methods:

Four groups of patients were selected from a database of autopsies performed at Great Ormond Street Hospital, London between 1996 and 2006. The groups comprised 20 infants dying from proven infection, 10 infants dying from sepsis, 10 infants dying with no explanation (i.e. SIDS), and 10 infants dying of non-infectious causes (e.g. trauma). Tests for 53 known inflammatory markers and markers identified in a previous study were developed with targeted proteomics using tandem mass spectrometry. These were applied to formalin-fixed paraffin-embedded post mortem liver from the selected patients. Statistical analysis was performed to assess differences in expression between groups.

Results:

26/53 markers could not be measured in the patient samples, 15/53 showed no significant difference between groups, and 12/53 showed a significant difference between groups. While some markers showed expected increased expression in cases of infection vs. controls (e.g. CRP), four pro-inflammatory cytokines showed a decrease in expression vs. controls (interleukin 1-alpha, interleukin 2, interleukin 6, and ICAM-1).

Conclusions:

The study demonstrates that in infants dying of infection, some pro-inflammatory cytokines are downregulated and it is possible that this represents a form of ‘immuneparesis’ contributing to rapid demise in these cases.
O2

Title:

Congenital plexiform cellular schwannoma: a "benign" but locally severely aggressive lesion.

Authors:
E Cheesman, A Kelsey, C Sethuraman, R Craigie, M Shah, B Brennan, R Santos

Background:
Hypothesis:
Aims:
Congenital plexiform cellular schwannomas were previously considered malignant peripheral nerve sheath tumours due to their hypercellularity, hyperchromatic nuclei and high mitotic activity. Recently it has been recognised that these lesions of infancy (and childhood) do not metastasise, though they are associated with a high rate of local recurrence. We describe two patients with congenital plexiform cellular schwannomas requiring radical disfiguring surgery, and we review the histological features.

Materials and Methods:
The first is a boy who presented at 1 month of age with a 3.6 cm penile mass. At two months of age he underwent tumour resection, and had multiple local recurrences, requiring three further resections at 6, 8 and 17 months. This resulted in significant disfigurement requiring formation of a neo-phallus. The second patient is a boy who presented at birth with a small cutaneous lesion of the lower leg. This rapidly increased in size to approximately 11.5 cm, and he was found to have a further lesion in the left popliteal fossa. He is due to undergo an above-knee amputation.

Results:
Both lesions showed similar histological features, and were particularly hypercellular, with wavy spindle cells containing hyperchromatic nuclei, and showing brisk mitotic activity. Tumour cells were diffusely positive for S100 and SOX-10.

Conclusions:
We conclude that, while congenital plexiform cellular schwannomas tend not to metastasise, their extremely aggressive local behaviour and rapid growth may require life-changing surgical intervention. Paediatric pathologists should be aware of this entity, and as well as avoiding overtreatment by misdiagnosis as malignant peripheral nerve sheath tumours, we should not be complacent simply because these lesions are described as “benign”.

Title:
The intercalated disc in paediatric patients with dilated cardiomyopathy.

Authors:
Elise L Kessler1, Peter GJ Nikkels2, Toon AB van Veen1
1: Department of Medical Physiology, 2: Department of Pathology, University Medical Center Utrecht, The Netherlands

Background:

Hypothesis:
Aims:
Dilated cardiomyopathy (DCM) leads to contractile dysfunction and disturbed force transduction, and is associated with substantial mortality in all age groups. Involvement of the intercalated disc (ID) has been reported in various cases. In this study, we aimed to illustrate subcellular alterations in children diagnosed with DCM compared to age-matched controls. We focused on proteins of the intercalated disc (ID) that are known to be crucially stable under healthy conditions and destabilized during cardiac injury in adults.

Materials and Methods:
Paediatric specimens were collected from ventricular tissue of 7 individuals diagnosed with DCM (age ranging from a gestational age of 23 weeks to 7 weeks postnatal) and age-matched controls that died of non-cardiovascular cause. We determined the amount of fibrosis and localization of proteins of the adherens junction, desmosomes and gap junctions and the sodium channel Nav1.5 by immunohistochemistry.

Results:
This study revealed that in paediatric DCM patients, most proteins follow the same spatio-temporal changes in subcellular localization when compared to controls. However, the desmosomal protein Desmoglein-2 was reduced in all paediatric DCM specimens, but not in controls or adult DCM patients. Endocardial, transmural and epicardial fibrosis was increased in all paediatric patients when compared to age-matched controls.

Conclusions:
Cardiac composition of the ID in paediatric DCM patients is similar to controls, except of the location of Desmoglein-2 and the presence of severe fibrosis. This suggests that the architecture of desmosomal junctions is disturbed in DCM patients, even in very early stages of their lives. These findings contribute to understanding of molecular cardiac development during health and disease and progression of DCM in young children.
**Title:**

Generalized Arterial Calcification of Infancy with compound heterozygous mutations in the ATP-binding cassette, subfamily C, member 6 gene and a review of the literature

**Authors:**
Kathrin Ludwig1, Stefania Rizzo1, Rudy Celeghin1, Elisabetta Lazzarin1, Marco Cason1, Paolo Balli2, Gaetano Thiene1, Kalliopi Pilichou1, Cristian Basso1

**Background:**

Hypothesis:

Aims:

Aim of study: Generalized Arterial Calcification of Infancy (GACI), a rare autosomal recessive disorder, is characterized by diffused internal elastic lamina calcification and fibrotic-myointimal proliferation with stenosis of large/medium size arteries. Biallelic inactivating ENPP1-mutations account for most cases, while ABCC6-mutations are rare.

We report a case of GACI manifesting as sudden death at 6 years of age due to chronic ischemic heart disease with postinfarction aneurysm as a consequence of widespread arterial calcification at autopsy. Past medical history revealed recurrent epigastric angina.

We performed a literature review of this rare entity highlighting its importance in the differential diagnosis calcifications in infancy.

**Materials and Methods:**

Polymerase-chain-reaction products of ENPP1 (NM.006208.2) and ABCC6 (NM.001171.5) were sequenced bidirectionally on an ABI 3500Dx-platform and analysed by Alamut-software. Systematic literature review for GACI with homozygous/compound heterozygous ABCC6-mutations was conducted.

**Results:**

No ENPP1-mutations. Analysis of the ABCC6-gene identified two rare variants defined as “pathogenic” by in silico tools [c.2018 T>C (Leu673Pro); c.3836 C>T (Pro1279Leu)].

Literature search identified 12 other GACI-cases (median age at data collection 31 months): four died within the first three months of life. Diffused arterial calcification was present in 11/12 cases, while cardiovascular complications and additional anomalies were present in 9 cases, respectively. Histology was available only for 2/12 cases.

**Conclusions:**

Diffused arterial calcification in children is rare. Clinical presentation of ABCC6-GACI is highly variable and can be subtle, especially upon onset. However, prompt diagnosis is mandatory due to devastating clinical manifestations and possible bisphosphonate-treatment.
Title:

How does fetal brain/liver weight ratio vary by gestational age, degree of maceration and autopsy diagnosis?

Authors:

Bente Ediassen Opsjøn, Øyvind Salvesen, Christina Vogt
Department of Laboratory Medicine, Children’s and Women’s Health, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

Background:
Recent studies have shown that fetal body weight and organ weights decrease during intrauterine retention and between delivery and autopsy, and some organs lose weight more rapidly than others. As fetal bodyweight and certain weight ratios are used to evaluate growth restriction, this post-mortal weight loss must be taken into consideration to prevent overdiagnosing fetal growth disturbances.

Hypothesis:

Aims:
We aim to evaluate how the fetal brain/liver weight ratio (BLR) may vary by gestational age, degree of maceration and cause of fetal death.

Materials and Methods:
Autopsy reports from a selection of 209 non-anomalous fetuses with gestational age 12 weeks or more from singleton pregnancies were reviewed. Organ weights were recorded, and each case was classified according to degree of maceration. This was evaluated based on external description of the fetus, or, if not available, on the estimated intrauterine retention time. The effect of gestational age, maceration and cause of death was evaluated with univariate ANOVA tests.

Results:
Fetuses with a placental cause of death had significantly higher BLR than fetuses with an unknown cause of death. In addition, BLR increased with increasing degree of maceration. The variation due to gestational age was small and nonsignificant.

Conclusions:
Increasing maceration is associated with an increase in BLR. BLR may also differ between diagnostic groups. This must be taken into consideration when evaluating fetal growth restriction.
Title:
Morphological variants of necrotizing enterocolitis of newborns.

Authors:
Korchagina N.S., Nechaev L.V., Vorozhbieva T.E., Zhakota D.A., Tumanova E.L.
Pirogov Russian National Research Medical University, The N.F. Filatov Children’s City Hospital (Moscow, Russia)

Background:

Hypothesis:

Aims:
Necrotizing enterocolitis (NEC) is a polyetiological disease; risk factors include immaturity, hypoxia, bacterial colonization by pathogenic flora, inadequate enteral feeding[1]. NEC is characterized by high lethality (to 63%) [1,2, 3]. The aim of this research is to highlight the modern aspects of NEC, determine the morphological variants and its prediction of outcome in patients. One of the leading mechanisms of NEC pathogenesis is disturbance of gut microcirculation.

Materials and Methods:
We researched 40 infants: 31 biopsy and 9 post-mortem cases. 8 was were full-term (20,0%). 22 prematures (55,0%) was less than 32 weeks, and 16 (40,0%) with extremely low birth body weight. Patients were divided into groups by morphology changes: 1) predominant hemodynamic; 2) with a primary infectious-inflammatory; 3) mixed.

Results:
In the each group were evaluated the next parameters: the number of patients (12/5/23 respectively), the average gestational age (30,0±5,25/33,0±7,0/ 32,3±5,5 weeks respectively), the average weight at birth (1779,2±1179,8/2001,0±1348,7/1747,8±1078,8g), age at the time of formation of the clinic of peritonitis (17,3±17,8/ 40,0±47,1/ 20,8±17,6 days respectively), and mortality (41,7%/20.0%/31,8%).

Conclusions:
Thus, the most common version of the NEC was mixed, reflecting modern views on the etiology of the disease. The highest mortality was characteristic for hemodynamic variant and comprises 41,7%, required the minimum time for “acute abdomen” clinical manifestation and death. It should also be noted that there was a significant shift of the age of NEC development.
**Title:**

*Inner ear and Sudden Infant Death: Exploring Implications for disturbances in brainstem functions*

**Authors:**

Cohen Marta C (1), Donn Trudy (1), Rivolta Marcelo (2), Cacciabue Rivolta Daniela (2), Whitby Elspeth (3), Rubens Daniel (4).

**Background:**

Sudden Infant Death Syndrome (SIDS) remains the leading cause of infant mortality in Western societies. Neurobiological research identified important risk factors and potential mechanisms that could explain various aspects of the events leading to SIDS. Failure to arouse from a hypoxic/hypercarbic challenge is one of the key mechanisms underlying SIDS, and the inner ear appears an important piece surrounding some cases. A pilot study demonstrated altered newborn hearing test scores (Oto-acoustic Emission profile) in infants who subsequently died of SIDS. Our aim was to study the inner ear of infants dying of SIDS and compare it with an age-matched control group.

**Hypothesis:**

**Aims:**

**Materials and Methods:**

We used combined PM MRI/CT of temporal bone in cases presenting as SIDS. At PM, the temporal bone was retrieved. Anatomical exploration and histopathological analysis of the inner ear structures was performed using conventional H&E staining and INF of inner ear markers of the VIII nerve, such as b-tubulin III.

**Results:**

After the PM, 4c were SIDS and 4c became controls. The MRI/CT was normal in all cases. The organ of Corti was poorly preserved, with some hair cells lost to autolysis. Overall structure was normal. The spiral ganglion neurons and auditory nerve were reasonably well preserved. The histology was normal in 3 cases and 4 controls, but was abnormal in 1 SIDS case. In this, lymphoid tissue with germinal centers was found in the mucosa covering the middle ear, around the auditory nerve in the modiolus. With B tubulin, the nerve seems preserved. This coincided with a viral upper airway infection.

**Conclusions:**

Our study supports that inner ear dysfunction may affect some cases of SIDS, likely altering the hypercapnic ventilatory response and the arousal movements as seen in the wild-type mice with gentamycin-damaged inner-ears.
P6

Title:

Hippocampal anomalies of the dentate gyrus and sudden unexpected death in childhood

Authors:
Dr Victoria A Bryant, Professor Neil J Sebire and Dr Thomas S Jacques

Background:

Hypothesis:

Aims:
To test the hypothesis that hippocampal malformations are associated with an increased risk of unexplained sudden unexpected death in childhood.

Materials and Methods:
A retrospective study of hippocampal morphology in autopsy cases from the archives of Great Ormond Street Hospital from 2003-2015. Coronial and forensic autopsy cases of previously healthy children, >1 year old, who died suddenly and unexpectedly from any cause were identified and slides from hippocampus sections were retrieved. Cases from 2006 onwards were included if consent for research had been obtained at the time of autopsy. Hippocampi were assessed by an experienced paediatric neuropathologist blinded to the clinical features and cause of death. The hippocampi were assessed for specific dentate gyrus anomalies including focal granule cell bilamination (FGCB) and widespread granule cell dispersion (GCD). Any other anomalies identified were also documented.

Results:
Sixty-four cases of SUDC were included in the study; 39 explained (males 64%; age 367-6173 days) and 25 unexplained deaths (males 56%; age 435-6144 days). No cases of definite dentate gyrus anomalies were identified in either group - three cases were ‘suspicious’ for GCD/FGCB, two in the explained group and one in the unexplained group. Other findings were similar in both groups - two-thirds were normal and the remainder showing normal variants.
(Of note, GCD was found in three cases subsequently excluded due to known pre-existing neurological conditions).

Conclusions:
We suggest that hippocampal anomalies are more likely to be part of a generalised malformation syndrome and future work is planned to investigate this further.
Friday 8th September Afternoon Session

O3

Title:

Autopsy findings in concealed or denied pregnancy

Authors:
Dr SR Stenton, Dr MC Cohen

Background:
Hypothesis:
Aims:
Concealment or denial of pregnancy can occur in 1/475 pregnancies, posing serious risks to mother and baby. No autopsy case series of perinatal deaths with history of concealment or denial exists in the current literature. Our aim was to investigate the frequency of cases, maternal demographics and cause of death in this unique clinical scenario.

Materials and Methods:
Retrospective study based at a paediatric tertiary centre, reviewing all perinatal cases with a history of concealed or denied pregnancy from 2003-2016. Autopsy results, patient demographics and socio-economic factors were analysed.

Results:
During the study period the Coroner instructed 69 PMs in babies who had died in the first 24 hours of life. 17 (26%) were identified. The mean maternal age at delivery was 24.8 years. 50% of women had a partner and 33% had a previous pregnancy. Nine cases were full-term and remaining eight were from the second trimester. In 11/17 cases the baby died at hospital or at home. In the other 6, the infant was found hidden in a public space. The cause of death was unascertained in 8/17 cases and 4/17 cases were labelled as stillborn. In the remaining post-mortems, the cause of death was attributed to hypoxia, congenital infection or fetal abnormality.

Conclusions:
Autopsy examination with a history of concealment or denial of pregnancy is not an uncommon scenario for the paediatric pathologist. Assessing viability of the baby at the time of delivery is difficult but crucial to the investigation.
Title:
Necrotizing enterocolitis in twin pregnancies: relation with placenta anatomy.

Authors:
Rosan R. Aapkes1, Peter G.J. Nikkels2, Hens A.A. Brouwers3, Corine Koopmans-Esseboom3, Karien E.A. Hack1
1: Department of Gynaecology and Obstetrics, 2: Department of Pathology, 3: Department of Paediatrics, University Medical Center Utrecht (UMCU), Utrecht, The Netherlands.

Background:

Hypothesis:
Aim of study To evaluate the relationship between placentation, placental abnormalities and necrotizing enterocolitis (NEC) in multiple pregnancies. We hypothesized that unbalanced interfetal transfusion through vascular anastomoses in monochorionic placentation (MC) causes hypoperfusion of intestinal mucosa, increasing the risk for NEC development.

Materials and Methods:
We retrospectively selected all multiple pregnancies at the University Medical Centre Utrecht (UMCU), between January 1995 and December 2015. We compared baseline characteristics, neonatal and maternal outcomes of MC versus dichorionic placentation (DC). Secondly, we analysed MC pregnancy ultrasound and pathology abnormalities in relation to NEC development. Third, we compared illness characteristics of NEC related to chorionicity. Statistics were performed with SPSS.

Results:
We included 2859 DC neonates and 817 MC neonates. NEC is present more often in MC (3.3% MC versus 1.6% DC, P=0.003), even after correction for birth weight, gestational age and nulliparity (OR 1.7, 95% CI 1.0-2.8). We did not find a significant relation between ultrasound abnormalities and NEC. However, the presence of NEC is related to the absence of AA-anastomoses (64.3% in NEC, 84.4% in no-NEC, p=0.044) and the presence of unbalanced interfetal transfusion (71.4% in NEC, 32.4% in no-NEC, p=0.002). In case NEC illness after MC pregnancy, there is a trend for more surgery (72.7%, versus 46.2% in the DC group).

Conclusions:
NEC is more common after MC pregnancy and related to the presence of unbalanced arterial-venous anastomoses, without stabilizing arterial-arterial anastomoses. Probably, subtle ischemic damage due to intra uterine foetal hypotension will play a key role in the development of NEC.
**Title:**

**LIMB BODY WALL COMPLEX: DEFINITION AND DISCUSSION OF ETIOPATHOGENESIS. A 8-YEAR TRICENTER STUDY.**

**Authors:**

Ana Costa Braga1,2, Lucília Monteiro3, Paula Borralho Nunes1,4, Marco Ferreira1, Sophie Collardeau-Frachon5,6

1Pathology Department, Hospital Professor Doutor Fernando Fonseca, EPE, Amadora, Portugal

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5Institut de Pathologie EST, Centre Hospitalier et Universitaire de Lyon - Hôpital Femme-Mère-Enfant, Lyon, France

6Faculté de Médecine Lyon Est, Université Claude Bernard Lyon 1, Lyon, France

**Aims:**

Limb body wall complex (LBWC) is a rare and fatal congenital condition defined by the presence of 2 or 3 defects involving encephalon, abdominal wall and limbs. Etiopathogenesis is still unknown. Several hypotheses have been suggested: early amnion rupture, embryonic circulatory failure and embryonic dysgenesis. Our aims were to review a large cohort of LBWC in order to characterize the defects and to look for predisposing factors (placenta anomalies, maternal background).

**Materials and Methods:**

Cases were collected from 3 centers for 8 years. Autopsy and placenta reports and maternal and obstetric history were reviewed for each case.

**Results:**

28 cases of LBWC out of 5965 autopsies have been reviewed (0.5%). Average gestational age was 15 weeks and average maternal age was 31 years (19 - 44 years). Body defects involved both limbs and abdominal and/or thoracic wall in 42,9%. Exencephaly/encephalocele were more frequently observed in association with limb defects than with abdominal wall defects. Visceral malformations occurred in 78,6% (urinary system in 32,1%). Placenta anomalies were present in 62%: 37% amniotic bands; 72,2% short cords; 47,4% cords with amniotic membranes; 45% single umbilical arteries. Preliminary results about maternal and obstetric history didn’t show any specific association.

**Conclusions:**

LBWC is a heterogeneous condition, associated with a high incidence of short and single umbilical artery. Our results favor a primary developmental defect of the embryonic disk.
Title:
Positive immunostaining for ATRX protein in neuroblastoma – does it exclude an ATRX gene mutation?

Authors:
Rose Chami, Anthony Arnoldo, Paula Marrano, Mary Shago, Paul Thorner.
Institution: Divisions of Pathology and Genome Diagnostics, Department of Paediatric Laboratory Medicine, Hospital for Sick Children, Toronto, Ontario, Canada. Department of Laboratory Medicine and Pathobiology, University of Toronto, Ontario, Canada.

Background:
Neuroblastoma is the most common extracranial solid tumour of childhood and is characterized by a heterogeneity in histology and molecular biology that is reflected in its clinical outcome. The ATRX protein is involved in chromatin remodelling, nucleosome assembly, and telomere maintenance. ATRX mutations are associated with stage-4 neuroblastoma and an older age at diagnosis. Patients with ATRX mutations have a more chronic and progressive course of disease. Screening older neuroblastoma patients at diagnosis for ATRX mutations may help identify those who might not respond well to standard therapy and might benefit from more personalized therapy. Mutations are believed to result in loss of ATRX protein, which can be detected by immunohistochemistry as loss of nuclear staining.

Hypothesis:
Aims:
Our aim was to investigate whether positive staining can occur in the presence of mutation in ATRX gene.

Materials and Methods:
We screened 30 cases of neuroblastoma by SNP array and immunostaining for ATRX.

Results:
All cases showed retention of ATRX expression by immunohistochemistry. Two cases showed a deletion involving the 5’ end of the ATRX gene by SNP array. The ATRX antibody recognises an epitope at the C terminal region. Presumably in these cases, an in-frame deletion occurred, and a truncated protein resulted with the C terminal intact.

Conclusions:
While negative immunostaining for ATRX is considered to reflect a mutation in ATRX, positive immunostaining does not rule out the possibility of a mutation and molecular genetic testing in some form should be carried out, particularly for older neuroblastoma patients.
Title:
An analysis of the Relevant Condition at Death (ReCoDe) found in a series of Minimally Invasive Postmortems. How does it compare to the traditional Invasive Postmortem?

Authors:
Rachel Rummery, Jessica Agius De Giovanni, Ashok Raghavan, E Whitby, Marta C Cohen. Histopathology and Radiology Departments, Sheffield Children’s Hospital, Western Bank, Sheffield, S10 2TH, United Kingdom.

Background:
Hypothesis:
Aims:
To determine what percentage of cases in a series of minimally invasive postmortems gave a ReCoDe other than I1 (no cause of death found). We also aimed to compare this with published ReCoDe rates for traditional postmortems, to determine which element of the post-mortem was most significant in providing the ReCoDe and the relative numbers of different ReCoDe classifications within our population.

Methods:
We gathered our series from the mortuary electronic database from 2012-2017, where minimally invasive postmortems are recorded with a separate denominator. We included all intrauterine fetal deaths, early and late neonatal deaths, up to 28 days of age. We found 76 cases ready to analyse and analysed these cases against preprepared parameters on an Excel spreadsheet.

Results:
We found that a ReCoDe other than I1 was found in 66 cases out of 76 (85.5% of the total). This compares to a rate of 85% in published series of traditional postmortems. The most important element of the minimally invasive post-mortem in providing the ReCoDe was the placenta in 45 cases (59%), followed by the MRI in 17 cases (22%). External examination was most important in 2 cases (3%), and karyotype in 2 cases (3%). The skeletal survey, whilst providing valuable contributory information, did not provide the ReCoDe in any cases. 10 cases (13%) were coded as I1.
The commonest ReCoDe was A1 (18 cases, 23%) followed by D1 and C4 (13 cases, 17% each) and I1 (10 cases, 13%). There were 6 cases of B2 (8%), 5 cases of B4 and C5 (7% each), 2 cases of C1 (3%) and 1 case each of A2, A6, A8 and G1 (1% each).

Conclusions:
Minimally invasive postmortems provide a good alternative to traditional postmortems to those families who do not wish to proceed with an invasive post-mortem, providing comparable ReCoDe rates.
Title:

TAYBI-LINDEN syndrome - Variability of the fetal phenotype

Authors:

C.Fallet-Bianco, F.Rypens, MA Delrue, M.Jovanovic, N.Patey, LL.Oligny

Background:

Taybi-Linden syndrome is a rare autosomal recessive disorder that belongs to the group of microcephalic osteoplastic primordial dwarfisms (MOPD), also known as MOPD type I and III as delineated by Majewski et al. (1982). It is characterized by intrauterine growth retardation (IUGR), skeletal dysplasia, dysmorphic facial features, anomalies of brain development and caused by mutations in RNU4ATAC. Antenatal descriptions are rare.

Hypothesis:

Aims:

Materials and Methods:

We report 4 fetuses from 2 unrelated families and non consanguineous parents. After prenatal diagnosis, on US and MR (2cases), TOP was performed at respectively 21, 34, 22 and 16 weeks of gestation (GW). Caryotype was normal in all. In 3 fetuses, post mortem examination was performed including skeletal X-rays and detailed neuropathological study.

Results:

Both fetuses of family 1 demonstrated unusual features. The first 21-GW fetus presented with IUGR, skeletal dysplasia and moderate microcephaly with callosal agenesis, while the second 34-GW fetus showed a severe microcephaly with simplified gyral pattern and moderate IUGR without significant skeletal dysplasia. In family 2, the first 22-GW fetus demonstrated typical features associating precocious and severe IUGR, skeletal dysplasia, suggestive facial dysmorphia, microlissencephaly and was found mutated in RNU4ATAC. A second fetus was diagnosed early by molecular testing at 15 GW and TOP performed at 16 GW by curettage. Mutations of RNU4ATAC were also found in both fetuses of family1.

Conclusions:

We provide description of 3 fetuses, mutated in RNU4ATAC, with Taybi-Linden syndrome demonstrating a significant variability of the fetal phenotype in different families but also in the same family.
Title:
Chorionic villi genotyping of fixed and paraffin-embedded tissues in molar and non-molar pregnancies

Authors:
Alfons Nadal, Carlota Rovira*, Laura Magnano, Mireia Garcia, Elena Gonzalvo, Sandra Martinez and Marta Aymerich
Hospital Clinic and *Hospital de Sant Joan de Déu, Barcelona, Spain

Background:

Hypothesis:

Aims:
To analyze the feasibility of villi genotyping from formaldehyde-fixed, paraffin embedded tissues in the differential diagnosis of gestational trophoblastic disease.

Materials and Methods:
53 cases (22 molar and 31 non-molar) were analyzed with the Mentype Chimera PCR amplification kit. Products were run in Avant 3130 or 3130XL DNA sequencers and analyzed with ChimerisMonitor 2.0. In 34 of the cases maternal tissue was also analyzed. Conventional cytogenetics were available in 19 cases. For intraobserver agreement assessment, electropherograms were re-analyzed after a 6 months wash out period.

Results:
Electropherograms satisfactory for analysis were obtained in 51 cases (96%). Genotypes were classified as triploid or non-triploid. When maternal tissue was analyzed, genotypes were subclassified as triploid diandric (consistent with partial mole), triploid diginic, non-triploid biparental, or non-triploid monoparental (consistent with complete mole) Genotyping was concordant with conventional cytogenetics in 18 out of 18 cases (100%, one case was not satisfactory for the analysis). Intraobserver agreement was 94% (33 out of 35). Genotyping results changed the original diagnosis in at least four cases: three cases changed from dysmorphic villi to partial mole, and one case changed from partial mole to dysmorphic villi. Genotyping detected additional chromosomal anomalies in non-triploid cases that could be related to pregnancy loss in eight cases(trisomies 3 -twice-, 7 and 8 -in three cases each-, and 21 -altogether with a trisomy 7-). Four cases required resampling to purify tissue from contamination.

Conclusions:
Genotyping of chorionic villi can be efficiently achieved from formaldehyde-fixed, paraffin-embedded samples as a tool in the differential diagnosis of molar pregnancies. Sample purity is essential.
Title:

Mitochondrial respiratory chain disease presenting as sudden unexplained death in infancy (SUDI) and Childhood (SUDC)

Authors:
1 Histopathology, Sheffield Children’s Hospital, Sheffield; 2. Clinical Chemistry, Sheffield Children’s Hospital; 3. Neurometabolic Unit, National Hospital for Neurology, Queen Square, London; 4. Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Oxford; 5. Wellcome Trust Centre for Mitochondrial Research, Newcastle; 6. University of Sheffield, Institute for Translational Neuroscience (SITraN), Sheffield; 7. Great Ormond Street, London, UK

Background:
Disorders of mitochondrial respiratory chain (MRC) function represent one of the commonest inherited metabolic diseases. Over 1,000 genes are involved in the expression of a functional respiratory chain. The contribution of MRC disease to SUDI is unknown.

Our protocol of investigation of SUDI includes fatty acid oxidation flux (FAOF) in post mortem cultured fibroblasts. This allows detection of primary inherited defects of mitochondrial ß-oxidation. Secondary reduction of FAOF flux serves as a marker for altered oxidative metabolism/altered redox state within the cell and may serve as a surrogate marker for MRC disease.

Hypothesis:

Aims:
We aimed to analyse those cases of SUDI/SUDC that demonstrated reduced FAOF.

Materials and Methods:
FAOF was assayed in cultured fibroblasts by measuring the release as 3H20 from labeled substrates.
Results were reported as nmol/mg fibroblast protein/hour and expressed as percentage of the mean of simultaneous controls. Mitochondrial DNA (mtDNA) depletion studies were by Pico Green staining and assessment of redox state was by Mitotracker/Tetramethylrhodamine methyl ester (TMRM). Fibroblast complexes were measured by spectrophotometric methods.

Results:
We investigated >1800 cases of SUDI in the last 20 years. 29c had an abnormal FAOF, strongly suggestive of an underlying MRC disorder. 11/29c underwent post mortem examination at our institutions. 8 were male and 3 females, between 8 days and 20 months. 7c corresponded to SUDI or SUDC. In 1c each there was: cerebellar haemorrhage, pulmonary haemorrhage, bronchopneumonia and non-compaction cardiomyopathy. In 5c there was mosaic mtDNA depletion in fibroblasts and a single POLG mutation of uncertain significance in one. Complex II was reduced in 2c and complex IV in another 2c.
Conclusions:
1.6% SUDI/SUDC have low FAOF suggesting abnormalities of MRC function.

P7

Title:
Sudden Cardiac Death in Infancy and Childhood: findings from 20-years of autopsy

Authors:
Dr Victoria A Bryant and Professor Neil J Sebire

Background:
Hypothesis:
Aims:
To determine the relative incidence, aetiology and presentation of sudden cardiac death (SCD) in infancy and childhood.

Materials and Methods:
An observational study of 2,432 paediatric autopsies performed on behalf of Her Majesty’s Coroner at Great Ormond Street Hospital from 1996-2015. SCD is defined as sudden unexpected death due to cardiac pathology identified at autopsy.

Results:
There were 121 SCDs (5%) and most were in infants under 1 year, n=78 (65%). Myocarditis was the commonest pathology, n=43 (36%) with viral infection confirmed in 45% (Parvovirus B19 63%; Enterovirus 26%). Congenital heart disease (CHD) and cardiomyopathy accounted for 32 cases each (26%). For these three diagnoses, there were significant differences in the median age (in days) at presentation; 539 vs 175.5 vs 9 - myocarditis, cardiomyopathy and CHD respectively (p<0.0001). All CHD, bar one, occurred in infants aged <3 months. Prodromal signs/symptoms, if present, were mostly non-specific and reported more frequently in myocarditis. A significant past medical history was reported in four, three of whom died from coronary artery disease and one with myocardial necrosis (aetiology unknown).

Conclusions:
SCD is rare in the paediatric population with most individuals displaying no signs/symptoms until acute deterioration in the final 24 hours of life. These findings support recent observations of an increasing role of Parvovirus in myocarditis - prevention strategies (vaccination) may be the only means of reducing this burden. Occult CHD remains the commonest cause of SCD in infancy and further developments in screening are required to improve early detection.
Title: High feto:placental ratio constitutes an independent risk factor for stillbirth

Authors: Heaford A, Mechler C, Karaa E. Scheimberg I.
Royal London Hospital, Barts Health NHS Trust, London, UK.

Background: Hypothesis: Aims: Feto:placental weight ratio (FPR) is considered an indicator of intrauterine fetal nutrition and has been associated with adverse outcomes such as IUGR, perinatal distress and development of chronic diseases in adulthood. We compared FPR with perinatal outcomes to determine an association between FPR centiles and outcome.

Materials and Methods: Retrospective review of 519 consecutive stillbirth (SB) and early neonatal death (ENND) placentas were compared with 335 livebirth (LB) placentas.

Results: FPR in 71% of SB/ENND was in 10-90th centile. 15% were <10th centile (low FPR) whilst 14% were >90th centile (high FPR). High FPR was more common in SB/ENND than in LB. High FPR was more common at or near term. Low FPR was more frequent in SGA (19%) than in AGA (12%) and LGA (11%) babies. High FPR was more common in LGA (26%) than in SGA (20%) and AGA (19%) babies. With the exception of FPR between 75-90th centile, no significant pathology was the most common placental finding in all groups. A linear relationship was not observed between FPR and any specific pathology.

Conclusions: High FPR is more frequent in SB/ENND than in LB. It is more common in fetuses delivered at term or large for gestational age. No relationship was identified between FPR centile and placental pathology. The histology of high FPR placentas was not significantly different from the placentas with lower FPR indicating a high FPR centile may be an independent risk factor for stillbirth regardless of placental histology and baby’s size.
Title:

Mixed maturation patterns - when acceleration meets delay.

Authors: Yvonne McCartney, Marie Culliton, Paul Downey, Eoghan E. Mooney.

Background:

Hypothesis:

Aims:

Placental maturation that is appropriate for gestation is important in ensuring optimal fetal development. An accelerated maturation pattern reflects maternal vascular malperfusion (MVM), the leading cause of perinatal loss, seen in approximately one third of cases. Delayed villous maturation (DVM) has also been associated with perinatal loss and is reported in 5 – 7% of placentas. A combination of both accelerated and delayed maturation patterns could be expected in a number of cases. The aim of this study was to compare a cohort of placentas diagnosed as DVM or as a mixed pattern (features of both accelerated and delayed maturation).

Materials and Methods:

Cases with a diagnosis of DVM (n = 116) and those with a diagnosis of a mixed pattern (n = 116) were selected from the pathology database between 2013 and 2016. Cases were reported by a single experienced placental pathologist. Gross details were recorded, including cord insertion, cord coiling and the presence or absence of placental disruption. Clinical details obtained included maternal age and parity, mode of delivery, gestation at delivery, birth weight and infant gender.

Results:

Groups were comparable in terms of gestational age, gender and mode of delivery. Disruption of the maternal surface was similar in both groups. Cases with a mixed maturation pattern showed a statistically significantly smaller placenta size (fetoplacental weight ratio p value 0.0113) and lower birth weight (p value 0.0263).

Conclusions:
**Title:**

Microvillus inclusion disease: A clinicopathological study of three cases.

**Authors:**

**Background:**

**Hypothesis:**

**Aims:**

Microvillus inclusion disease (MIC) is a leading cause of secretory diarrhea in the first weeks of life. Hereby we present three cases of this rare disease.

**Materials and Methods:**

Case 1 was a three month-old boy presenting with watery diarrhea since first week of life. He was born at 36 gestational weeks as the third child of consanguineous parents and had one sibling died of similar complaints. As a part of investigation for chronic diarrhea a duodenal biopsy was done.

Case 2 was a two month-old boy admitted to the hospital with watery diarrhea since two weeks of life. He was a term baby and his parents were non-consanguineous. He died of septic shock at 7th day of hospitalization during investigation. A complete autopsy was performed.

Case 3 was a three month-old girl presented with metabolic acidosis, watery diarrhea and hypernatremic dehydration. She was born at 36 gestational weeks by caesarean section as 5th child of consanguineous parents. She had severe metabolic acidosis refractory to the treatment and died of sepsis at 44th day of life. A duodenal biopsy was done before death.

**Results:**

Light microscopy of duodenum was compatible with MIC in all cases and electron microscopy confirmed the diagnosis. Mutation analysis showed IVS10-2A > G (c.1323-2A>G) mutation of the MYO5B gene as homozygote in Case 3.

**Conclusions:**

MIC should be specifically considered in the differential diagnosis of neonatal onset severe diarrhea and intractable metabolic acidosis.
Title:
Preliminary Data on the Impact of Maternal Smoking During Pregnancy on Human Fetal Kidney Development

Authors:

Background:
Fetal smoke-exposure is linked to post-natal renal deficits, including smaller kidneys in humans, and reduced podocyte numbers in rats, possibly due to perturbed development. An analysis of renal developmental genes may help decipher the potential reasons for this.

Hypothesis:

Aims:
To establish a method to quantify glomerular podocytes in the human fetus and investigate the impact of maternal smoking on renal developmental gene expression.

Materials and Methods:
Morphometric analysis was developed (Formalin-fixed kidney sections, 10 fetuses: 11-17 weeks of gestation) using dual WT1/CD56 immunohistochemistry. Developmental mRNA transcripts (13) from 28 human fetal kidneys (8-20 weeks of gestation, male n=18, female n=10) from electively terminated normal pregnancies (REC 15/NS/0123) were quantified by RT-qPCR (normalised against PPIA). Linear regression models were used to analyse gestation- and smoke-related changes.

Results:
Morphometric analysis was successfully developed to quantify podocyte number per glomerular area. Five transcripts decreased (GDNF, WNT4, PAX2, FGF2, BMP7) and four increased (RET, WNT11, MME, NPHS2) with advancing gestation. Smoke-exposed fetuses had higher SPRY1 expression (P=0.029). A positive relationship between GDNF and SPRY1 in controls was lost in smoke-exposed fetuses.

Conclusions:
Using our newly established method, we will perform morphometric analysis in larger numbers of fetuses. Developmental transcripts vary with gestation, possibly reflecting roles at different points in development. Potential dysregulation between GDNF/SPRY1 and increased expression of inhibitory SPRY1 in smoke-exposed fetuses potentially will lead to greater inhibition of ureteric bud induction. A larger study is required to investigate the role of the GDNF/RET/WNT11 pathway in normal and smoke-exposed human fetal kidney development.
Hyperechogenic bowel and congenital CMV infected fetuses.

Authors:
Liliana Gabrielli,a Maria Paola Bonasoni,b Giuliana Simonazzi,c Donatella Santini,d a Claudia Pavia,a Tiziana Lazzarotto,e

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Background:
Hypothesis:
Aims:
Prenatal ultrasound findings in fetuses with CMV infection may include hyperechogenic bowel.
The objective of our study was to find a possible pathophysiology underlining hyperechogenic bowel in congenital CMV infected fetuses.

Materials and Methods:
We examined small and large intestines in 8 fetuses at 22 weeks of gestation with congenital CMV infection. Fetal diagnosis of CMV infection was based on CMV positivity in amniotic fluid by culture and Real Time PCR. Ultrasound findings showed four fetuses with hyperechogenic bowel and two of them with brain abnormalities. The other 4 fetuses had no ultrasound anomalies. Serial sections of duodenum, jejunum, ileum, large bowel were submitted for histological examination. Immunohistochemistry for CMV and lymphocytic infiltrate were also performed.

Results:
In the 4 fetuses with hyperechogenic bowel, macroscopic autopsy showed dilatation of the distal intestine, especially ileum and large bowel. Meconium appeared thickened and distally localized. Microscopic examination showed intestinal ganglioneuritis with CMV positive cells in the intestinal ganglia surrounded by a lymphocytic infiltrate mainly composed of cytotoxic T CD 8. CMV positive ganglion cells were observed only in the Auerbach's myenteric plexus through all different intestinal regions. Moreover, meconium granules within the enterocyte cytoplasm facing the intestinal lumen were observed. These may represent indirect signs of reduced intestinal peristalsis.
In the 4 fetuses with no hyperechogenic bowel, macroscopically the intestine was not dilated and intestinal sections showed either no CMV cells or inflammatory infiltrate.

Conclusions:
Hyperechogenic bowel probably can be explained primarily as reduced intestinal motility due to CMV ganglioneuritis in the Auerbach's myenteric plexus.

**P13**

**Title:**

*Development of a Novel Multiplex Post Mortem Test for Tissue Infection and Sepsis in Infants Using Tandem Mass Spectrometry.*

**Authors:**

Andrew R Bamber, Wendy Heywood, Kevin Mills, Neil J Sebire

**Background:**

Infection is the commonest cause of explained Sudden Unexpected Death in Infancy. There is increasing demand from parents to limit autopsies, but this is hampered by a lack of reliable tests for infection. This study aimed to develop a reliable post mortem test for infection/sepsis.

**Materials and Methods:**

Four patient groups were selected from a database of autopsies performed at Great Ormond Street Hospital from 1996-2006. They comprised 20 infants dying from proven infection, 10 dying from sepsis, 10 dying with no explanation (i.e. SIDS), and 10 dying of non-infectious causes (e.g. trauma). Tests for 53 known inflammatory markers/markers identified in a previous study were developed with targeted proteomics using tandem mass spectrometry. These were applied to formalin-fixed paraffin-embedded post mortem liver from the selected patients. Statistical analysis was performed to assess differences in expression between groups.

**Results:**

27/53 markers were measurable in patient samples and of these, three showed a statistically significant increase in infection/sepsis. Positivity for any two of C-reactive protein, Heat shock cognate 71 kDa protein (HSPA8), and Heat shock 70 kDa protein 1-like (HSPA1L) had a 90% specificity and 88.9% sensitivity for identification of infection. Levels of HSPA1L were markedly raised in sepsis (HSPA1L level >30 times control showed sensitivity 85.7%, specificity 88.9%).

**Conclusions:**

This multiplex test using CRP, HSPA1L and HSPA8 is a reliable and accurate test which allows identification of/distinction between tissue infection and sepsis in infants. This may be useful as part of minimally-invasive autopsy and in the living.
Title:

Unusual fetal akinesia with caudal dysgenesis expanding the spectrum of MNX1 mutations

Authors:

Background:
MNX1 gene is responsible for Currarino syndrome, a dominant inherited disorder characterized by sacral agenesis, presacral mass and anorectal malformation with variable expressivity, sometimes, asymptomatic. We report a severe, atypical case of fetal akinesia associated with a sacral agenesis and anorectal malformation resulting from a mutation of MNX1.

Hypothesis:

Aims:

Materials and Methods:
During the 5th pregnancy of consanguineous Egyptian parents, US detected a short spine with akinesia. The male baby, born at term, died within minutes after birth. Karyotype was normal. Previous history demonstrated a precocious miscarriage and 3 siblings died shortly after birth.

Results:
Post mortem examination demonstrated a fetal akinesia sequence including a significant IUGR, dysmorphic facial features, contractures of shoulders, hips, knees and ankles with amyotrophic legs and scoliosis associated with anal imperforation. Skeletal and visceral examination showed agenesis of lower ribs and lower lumbar vertebrae, sacrum and coccyx, renal, genital, colonic malformations and hypoplastic lungs. Neuropathological examination demonstrated a normal brain and a particularly short spinal cord with agenesis of lumbo-sacral segments as well as cauda equina. Previous siblings demonstrated a close phenotype, with anal imperforation and sacrococcygial teratoma in one. Whole Exome Sequencing (WES) demonstrated, in our case, a homozygous mutation in MNX1(HLXB9) gene, reported in rare cases of neonatal diabetes, but never in “classic” Currarino syndrome.

Conclusions:
This case showed the most severe phenotype never observed in MNX1 reported cases and emphasizes the usefulness of WES in prenatal diagnosis of fetal cases with an atypical or severe presentation different from that known in older subjects.
Saturday 9th September Morning Session

O 11

Title:

Macroscopic and Microscopic Placental Pathology in Stillbirths Versus Livebirths

Authors:
Heaford A, Mechler C, Karaa E. Scheimberg I.
Royal London Hospital, Barts Health NHS Trust, London, UK.

Background:
Hypothesis:
Aims:
Despite major progress in obstetric care stillbirth (SB) and early neonatal deaths (ENND) are still a problem. We compared the placetas of stillbirths/ENND to livebirths (LB) to identify risk factors within our population.

Materials and Methods:
Retrospective review of 519 consecutive SB and ENND placentas were compared with 335 LB placentas looking at gender, gestational age at delivery, appropriateness of fetal growth, feto:placental weight ratio and placental histology.

Results:
40% of SB/ENND and 55% of LB were born at term. Only 9% of LB were 24-27WG vs 29% of SB/ENND
Over 50% in both groups were appropriate for gestational age
High FPR was more common in the SB/ENND group than controls while low/normal FPR was more common in LB
No significant abnormality was common in both groups (SB/ENND 30%; LB 33%). Delayed maturation (14% vs 3%) and fetal vascular malperfusion (7% vs 2%) were more common in SB/ENND. Massive perivillous fibrin deposition and umbilical cord complications were seen in 2% and 6% of SB/ENND but were not present in LB, which showed more acute inflammation (25% vs 11%) and maternal vascular underperfusion (31% vs 26%).

Conclusions:
Perinatal death was more common in males, those born prematurely and those with a high feto:placental weight ratio centile. More than half of deceased infants showed appropriate growth for the gestational age. Although certain pathologies were more common in perinatal death, in 30% of cases no significant placental pathology could be identified to explain the death.
Investigating sudden unexpected death in childhood: the results of a 20-year autopsy study

To investigate the characteristics, autopsy findings and aetiology of sudden unexpected death in childhood (SUDC).

This is an observational study of 762 paediatric autopsies in children > 1 year, performed on behalf of HM Coroner at Great Ormond Street Hospital from 1996-2015 inclusive. SUDC refers to apparently healthy individuals without known pre-existing and potentially life-limiting conditions.

A total of 327 cases were classified as SUDC and 70% were in pre-school age children (1-4 years). The majority of SUDC were due to infectious causes (36%) with sepsis and respiratory tract infections accounting for nearly two-thirds of these. Non-infectious diseases were responsible for 24% and non-natural deaths (trauma-related, drownings, accidental asphyxia, suicides) accounted for 16%. There were 79 cases of unexplained SUDC of which 32 had potentially contributory autopsy findings – mostly indicative of infection - but deemed insufficient to fully explain the death. Fatal cardiac arrhythmia was suspected in 12 cases, mainly based on the circumstance of death, two of whom also had a positive family history.

Infectious disease remains one of the major aetiologies of SUDC, especially in pre-school age children. Most deaths occur out-of-hospital with minimal premonitory signs/symptoms indicating rapid progression of disease and suggesting an inadequate or aberrant host response. Despite complete autopsy, around 25% of SUDC remain unexplained, although infection is likely to be one of the main contributors in this cohort, highlighting the degree of investigational limitation.
Title:
Diagnostic Utility of Frozen Section in Paediatric Testicular and Paratesticular Lesions

Authors:
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Background:
Frozen sections are used routinely to assess suspected tumours in adults and aid surgical decision making. Similar application in paediatric tumours remains limited, especially in the evaluation of paediatric paratesticular lesions where diagnosis is reliant on clinical and imaging findings. Many benign paratesticular lesions in infancy and childhood may be difficult to distinguish from malignant lesions and result in unnecessary orchidectomy.

Hypothesis:

Aims:

Materials and Methods:
Retrospective of a series of 3 patients who underwent frozen section at the time of surgery for suspected testicular/paratesticular lesions were reviewed. Clinical information including age, histological diagnosis was recorded.

Results:
Case 1: 11-month old infant with a firm paratesticular mass not involving the testis. Rhabdomyosarcoma was suspected clinically and on imaging which was atypical. Intra-operative frozen section diagnosis confirmed a benign lesion (fibrous hamartoma of infancy). The mass was excised and the testis left in situ.
Case 2: 14 year old boy who presented with a large complex paratesticular mass closely abutting the entire testis. Even though radiologically it was suspected to be benign, the clinical features were suspicious and orchidectomy was thought to be the most pragmatic option. Frozen sections showed dysplasia of the rete testis and epididymis, confirmed by standard histology with no malignant changes.
Case 3: 9 year old with presented with chronic testicular pain, USS was suspicious of polar testicular lesion. Frozen sections showed normal histology and testis were spared.

Conclusions:
Frozen sections may accurately diagnose testicular and paratesticular masses. Though orchidectomy could be avoided only in case 1 and 3, frozen sections may aid surgical decision making with regards to sparing the testis in selected paediatric cases. Pathologists must endeavour to make themselves familiar with the potential advantages and limitations of frozen sections and the role of intraoperative frozen sections warrants further multidisciplinary evaluation.
**Title:**

Placental findings and perinatal deaths: a national review using consensus terminology.

**Authors:**

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**Background:**

Hypothesis:

Aims:

The National Perinatal Epidemiology Centre (NPEC) collects anonymised perinatal mortality data from all 19 Irish maternity units. Consensus terminology has been published to assist in reporting of placental pathology, and is now used in Ireland on a national basis. Placental pathology contributes to or causes stillbirth in 11 to 65% of cases in various classifications. Maternal vascular malperfusion (MVM) and fetal vascular malperfusion (FVM) play a major role. We assessed perinatal deaths where placental disease is the main cause of death, focusing on MVM and FVM.

**Materials and Methods:**

For the years 2014 and 2015, all cases of early and late neonatal deaths (regardless of gestation and birthweight at delivery) and stillbirths (≥24 weeks gestation or birthweight ≥500g) were included when placental disease was the main cause of death or an associated factor (n = 571).

**Results:**

MVM and FVM were reported in 73.7% and 77.9% of stillbirths and in 26.3% and 22% of neonatal deaths, respectively. There were 28 (5%) cases with both MVM and FVM. Both MVM and FVM were more common in males (57.5% and 55.2%). Co-existing pathologies included IUGR (3.9% of MVM) and cord pathology (9.5% of FVM).

**Conclusions:**

This is the first application of placental consensus terminology to national data of which we are aware. The frequency of placental pathology is consistent with previous studies. Our results highlight the major contribution to perinatal loss of MVM and FVM. The co-existence of MVM and FVM is an under-recognised phenomenon and is seen in 5% of cases.
Title:

Placental mesenchymal dysplasia: A case of clinical misdiagnosis and atypical p57 immunoexpression

Authors:
Dr S Stenton, Dr L Pipe, Dr J Stahlschmidt

Background:
Hypothesis:
Aims:
We present a case of placental mesenchymal dysplasia (PMD) which was initially misdiagnosed as partial mole (PM) on ultrasound and magnetic resonance imaging (MRI).

Materials and Methods:
A 29 year old para1+1 presented for her first scan at 13 weeks gestation (WGA). A large cystic placenta was identified with a normally formed fetus, suggestive of PM. Ultrasound at 17 WGA and an MRI at 22 WGA showed an enlarged placenta with multiple smooth-walled cysts. A CVS revealed a normal male karyotype. Clinically the impression was that of a PM. The patient developed pre-eclampsia and underwent an emergency caesarean section at 35 WGA with subsequent hysterectomy due to massive postpartum haemorrhage. The male infant was morphologically normal but small for gestation (1630g (3rd centile)).

Results:
We received a 1613g placenta (expected for gestation: 411g), measuring 22 x 19 x 7.5cm. Sections revealed multiple thin-walled cysts of variable size. Histology showed a mixed population of both grossly hydropic and small, normally formed chorionic villi. Cistern formation and thickened, muscular fetal stem vessels were seen. No trophoblastic proliferation or atypia was identified. Features of chronic fetal malperfusion were also noted. Immunohistochemistry for p57 was negative in mesenchymal stromal cells and trophoblasts, a feature which has not been previously described in PMD.

Conclusions:
A diagnosis of PMD should be considered in placentomegaly with a normally formed fetus. Mesenchymal cells are typically negative for p57 in PMD; here we present a unique case in which labelling for stromal cells and trophoblasts was negative.
Title:

Causes of clinically unexplained stillbirths referred for full post mortem examination to a perinatal centre in the United Kingdom between 2009-2015

Authors:

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Background:
Stillbirths (SBs) are the largest contributor to perinatal mortality. 1/200 babies are born dead (~5.2/1000 of total births). The overall adjusted stillbirth rate in the UK is 3.9 per 1000.
Postmortem (PM) examination of the baby and placenta has the highest diagnostic yield of all investigations. The Relevant Condition at Death (ReCoDe) classification is used to identify the relevant condition at the time of intrauterine death. The hierarchy starts from conditions affecting the fetus and moves outwards in anatomical groups, which are subdivided into pathophysiological conditions.

Hypothesis:

Aims:
To analyse the ReCoDe in a cohort of clinically unexplained SBs (USBs) after full PM examination.

Materials and Methods:
Reports for consecutive PMs from SBs referred to SCH during 2009 - 2015 were reviewed. In line with CEMACH definition, only SBs above 500 g and/or 24 gestational weeks were selected.
The analysis was restricted to cases in which the cause of the SB was unexplained to the obstetric team. Termination of pregnancies, cases with a known fetal or maternal condition causing IUD and limited or minimally invasive PMs were excluded.

Results:
258/2590 (10%) of all PMs corresponded to clinically USBs. 389 ReCoDe were identified in the 258 cases. After full PM, the causes were allocated to: placental insufficiency (37.5%), IUGR (24.5%), chorioamnionitis (14.1%), Umbilical cord abnormalities (12.3%), abruption (4.8%), foeto-maternal-haemorrhage (0.7%), maternal (0.2%) and unclassified (5.7%).

Conclusions:
Placental conditions (including umbilical cord and amniotic fluid abnormalities) are a major cause of SB, responsible of 68.7% of clinically unexplained SBs. IUGR and abnormal foeto:placental ratio are the other major contributor, accounting for 24.5%. A full PM is still the gold standard to help identify the cause of a SB.
Title:

Fine-needle aspiration cytology (FNAC) in children’s mycobacterial lymphadenitides

Authors:
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Background:
Atypical mycobacteriosis represent about 10% of pediatric non-neoplastic lymphoadenopathies in western countries. In the majority of cases the clinical and radiological presentation is clear, while in a significant minority the diagnosis requires tissue from the lymph-nodes involved, for pathological and microbiological investigations. Open biopsy is critical for the risk of nerve damage, pain, and surgical, aesthetic problems. In these cases, the use of FNAC is recommended to select patients for further investigations and/or to decide different treatments.

Hypothesis:
Aim of this study was to investigate the role of FNAC in the diagnosis of Mycobacterial lymphoadenopathies and to compare results with microbiological and histological findings.

Materials and Methods:
From the archives of Pathology and Pediatric Surgery Unit, Padova University Hospital, we retrieved the cytological, microbiological and histological data of 60 patients observed since 2013 till 2017, affected by cervical, submandibular, axillary and inguinal lymphadenopathy.

Results:
FNAC was performed in 36 cases and in 30 the material was sent for microbiology: 15/36 cases were positive for Mycobacterium infection, and cytology was represented by abundant necrotic material with granulocytes, lymphocytes, plasma cells, giant cells, macrophages. In 15/36 cases microbiology was negative. In 6/36 cases was impossible to obtain material for microbiological studies. Histology showed in all cases a granulomatous necrotizing process with numerous granulocytes.

Conclusions:
FNAC is the approach of choice in children with a suspect of atypical mycobacteriosis, is rapid, painless, can be repeated and sufficient to collect adequate material for microbiological studies.
Title:

Prospective study of rapid diagnosis of acute funisitis in placentas from neonatal intensive care babies.

Authors:

VR Sams, W Fullerton

Background:
Infection of neonates is a well recognised association of an adverse neurodevelopmental outcome. Placentas are often sent for histological evaluation in this setting but a routine 5 day turnaround time was felt to be too slow for clinical decision making since the presence of placental infection/acute funisitis was deemed by our neonatologists to be a critical piece of information when considering the cessation or continuous of antibiotic treatment at 48 hours of age.

Hypothesis:

Aims:

Materials and Methods:
We therefore studied placenta...