



The cover art of this abstract booklet is a representation of a student's journey through research. Starting with a basic understanding of science and its principles and progressing to learning the art of conducting 'blue sky' biomedical, translational and clinical research. The images represent the variety of research activities clinical academics enjoy throughout their careers, including laboratory and clinical research, teaching, education and nurturing the future generation of tomorrow's doctors.

Designed by Genevieve Marsh-Feiley; © Aberdeen Clinical Academic Training Scheme

Abstract Editors: Ross J Porter & Phyo K Myint

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Acknowledgement

On behalf of the recipients of the Aberdeen Summer Research Student Scholarship, the Executive Board of Aberdeen Clinical Academic Training (ACAT) Scheme would like to thank the financial contribution of the funders of the various undergraduate research scholarship programmes.

We also would like to thank Mrs. Janice Forsyth and Ms. Morag McConnell for their assistance with running the program. Special thanks to Genevieve Marsh-Feiley who created the cover art and Ross Porter who has contributed to the editing of this abstract booklet.

A handwritten signature in black ink, appearing to read 'Phyo K Myint', is centered on the page. The signature is fluid and cursive, with a large initial 'P'.

Professor Phyo K Myint
Director of Clinical Academic Training Development
& Chair, ACAT Executive Board

Aberdeen Research Scholarship Symposium, 28th November 2017
Venue: Suttie Centre Lecture Theatre and Atrium
17.30-20.45

Time	Speaker	Title
17.30-17.35	Prof. P K Myint	Welcome and Introduction
17.35-17.45	Ashan Jayasundera	Making the most of the Aberdeen Birth Cohorts' (ABC 1921, 1936, 1950) – A systematic review of how the data has been utilised in research
17.45-17.55	Dominika Boldovjáčová	New anti-fungal targets: bedside to bench
17.55-18.05	Duncan Ritchie	Can haematology blood tests at time of diagnosis predict response to neo-adjuvant treatment in locally advanced rectal cancer?
18.05-18.15	Mhairi McGowan	Determinants of Oral Health-Related Quality of Life in the institutionalised elderly: A systematic review
18.15-18.25	Tiberiu Pana	Myocardial infarction after stroke: time-dependent predictive co-morbid factors, incidence, and mortality
18.25-19.45	POSTERS	Refreshment, Poster Viewing and Assessment for ASRS Prize
19.45-19.55	Bernadine Chua	Maternal dietary fatty acid intake, body fatness, and <i>in vitro</i> fertilisation (IVF) outcomes
19.55-20.05	James Redmore	A novel murine model of conditional BSCL2 knockout in adiponectin-expressing cells: histomorphometric effects on the infra-patellar fat pad of the knee
20.05-20.15	Philip Cannon	Telemedicine: Patients' perspectives in the Aberdeen Royal Infirmary Gastroenterology out-patient setting
20.15-20.25	Samuel R Neal	High anticholinergic burden in middle-aged women is associated with recurrent falls in later life
20.25-20.30	Break	Assessment Panel Meeting
20.30-20.40	Prof. A Denison	ASRS Prizes
20.40-20.45	Prof. P K Myint	Wrap up and close

ASRS Poster Presentations

No.	Presenter	Title
01	Bilal Benzahia	Using MRI to determine whether percutaneous needle fasciotomy has a long-term effect on the volume of diseased tissue in palmar fascia of Dupuytren's patients
02	Dylan McClurg	Inter-pregnancy BMI change and the risk of preeclampsia (PE) and small for gestational age (SGA) babies: Analysis of the first two pregnancies in women from three European countries
03	Owens Iguodala	Oral Health Behaviours and Oral Health-Related Quality of Life (OHRQoL) in 18 – 25 year old young adults
04	Natalie Smellie	Improving access to fracture prevention services in island communities
05	Maria Soupashi	Association between breast cancer risk and characteristics and the dietary intake of fats and fat soluble vitamins
06	Ioannis Georgiou	The Central Vein Sign relationship to the blood-brain barrier in Multiple Sclerosis
07	Qaisar Khan	Incidence of dementia in Parkinson's Disease in the PINE study
08	Craig Fraser	Can telemedicine play a role in the delivery of Gastroenterology out-patient services in Aberdeen Royal Infirmary?
09	Nicole Lorking	Winter excess in hospital admissions, in-patient mortality, and complications in stroke: A Thailand National Database Study

HOTSTART Program & Endowed Scholarship Poster Presentations

No.	Presenter	Title
10	Caoimhin O'Higgins	Deciphering the role of regulatory CD4 T cells in oral and oropharyngeal cancer: a systematic review
11	Edward Bader	Probiotic supplementation for the treatment of behavioural & cognitive symptoms in neurodegenerative disease: A systematic review
12	Guillaume Mignot	CLEC12A inhibits inflammation and neutrophil extracellular trap formation in a context of murine collagen antibody induced rheumatoid arthritis
13	Haroon Ejaz	The major melatonin metabolite 6-hydroxymelatonin sulphate increases during pregnancy, associated with decreased oxidative stress
14	Mazen Allam	The effect of YAP knockout in joint inter-zone progeny on the mature skeleton

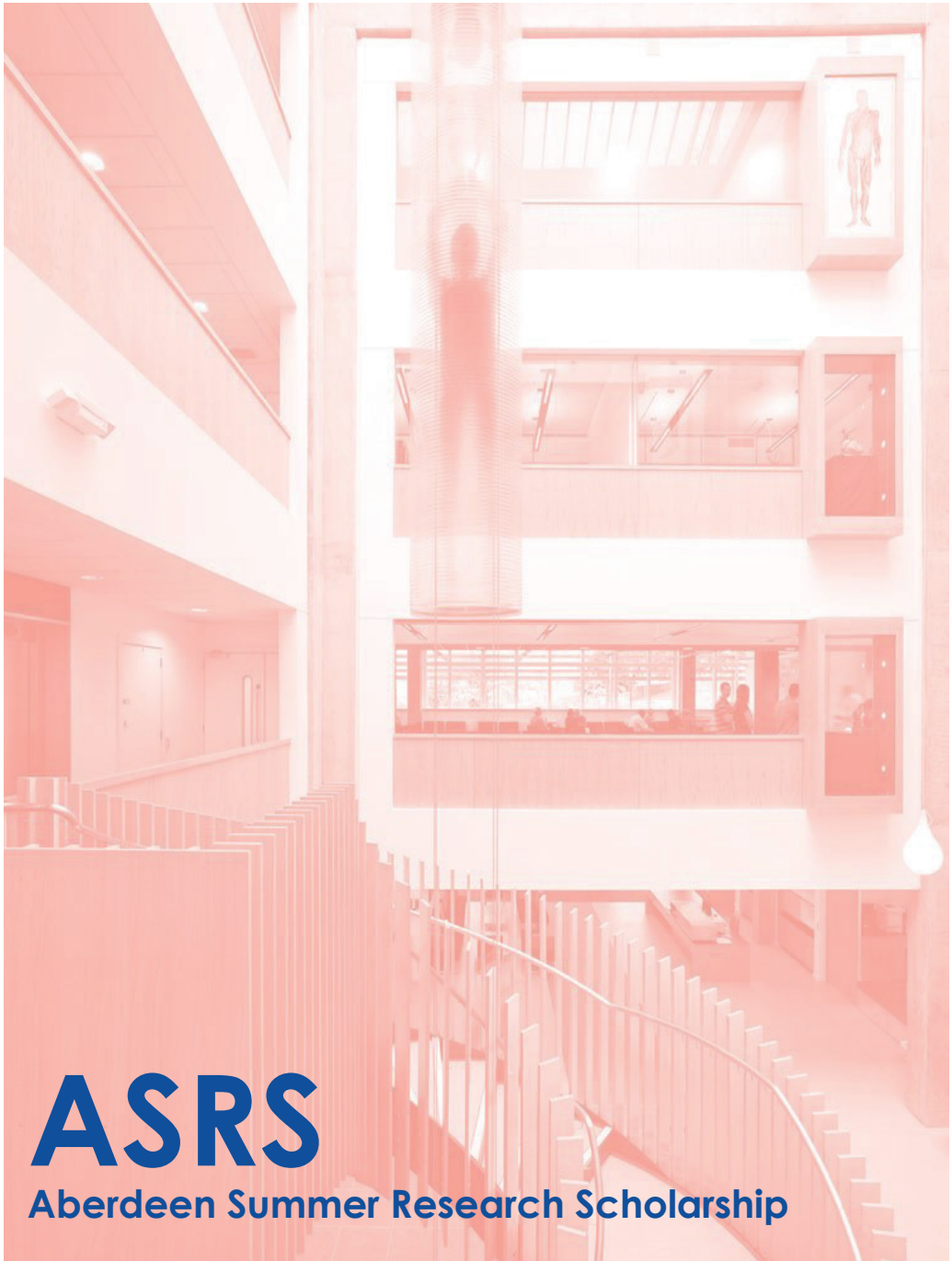
15	Fiona Craigen	Efficacy of cryoprecipitate versus fibrinogen concentrate in clot formation and stability: Implications for treatment of trauma induced coagulopathy
16	Letizia Delle Vedove	Characterisation of serotonergic cells in the brain
17	Kerri Palmer	The role of neuro-inflammation in Alzheimer's Disease progression
18	Thomas KM Ng	The inclusion/exclusion of Nonidet P-40 detergent to brain lysates affects
19	Nasir Rafiq	Role of cAMP and Epac in central nervous system neuronal growth; a comparative analysis between isolated neuronal cortex, spine and dorsal root ganglia cultures

Externally Funded Scholarship Poster Presentations

No.	Presenter	Title
20	long Man Tung	SMOM and Wnt- β -catenin asymmetry pathway in <i>Caenorhabditis elegans</i>
21	Samuel Kent	Does size and direction of osteotomy in orthognathic surgery affect risk of subsequent plate removal?
22	Sandra Hapca	The role of HMGB1 in the pathogenesis of colorectal cancer
23	Andrew Daniel Ablett	Cognitive impairment is associated with mortality in older adults in emergency surgical setting: Findings from the Older Persons Surgical Outcomes Collaboration (OPSOC)
24	Serena Banh	Effect of <i>in utero</i> exposure to cigarette smoking to human fetal kidney development

Abstract Only Presentations

Author	Title
Nayl Gilani	Cost of routine TSH testing in fertility clinics



ASRS

Aberdeen Summer Research Scholarship

Using MRI to determine whether percutaneous needle fasciotomy has a long-term effect on the volume of diseased tissue in palmar fascia of Dupuytren's patients

Bilal Benzahia

Background

Dupuytren's is a fibrosing condition which affects the subcutaneous tissue of the palm of the hand. Tense, fibrous cords and nodules form, usually (but not necessarily) across the metacarpo-phalangeal joints or proximal inter-phalangeal joints of the 5th and 4th digits. The result is a gradual loss of the ability to extend the fingers as they are held in a flexed position.

Most treatments involve surgery in order to remove the diseased tissue (fasciectomy), sometimes with the overlying skin (dermofasciectomy). Needle fasciotomy is a treatment which does not remove the tissue, but simply cuts the cords through small incisions under local anaesthetic to release the tension keeping the affected joints flexed. Although needle fasciotomy has a higher recurrence rate than other surgical interventions, it carries less risks, the patient recovers faster and is generally viewed as the best long-term treatment, especially in frail patients unsuitable for more traumatic surgery.

This study aimed to determine whether needle fasciotomy has a long-term effect on the volume of Dupuytren's tissue present in patients, with the secondary aim of assessing the suitability of MRI as a method of imaging Dupuytren's *in vivo*.

Methods

Tesla 3.0 MRI's of 5 Dupuytren's patients were taken before, 2 weeks after, and 6 months after undergoing needle fasciotomy. Using Philips DiCom software the scans were reformatted into millimetre thick "slices" perpendicular to the course of the cords. By manually measuring the area of diseased tissue in each of these slices, the total volume of Dupuytren's tissue, which has a low to intermediate signal intensity on MRI's, was calculated and plotted over time.

Results

Data analysis is ongoing.

Conclusion

It is expected that the volume of Dupuytren's tissue would be slightly reduced immediately after surgery, but by 6 months would have increased to its original value or greater, since needle fasciotomy works by relieving tension in the cords, not removing them.

Supervisors: Mr George Ashcroft, Mr David Lawrie, Mrs Claire Miller, Dr Gordon Waiters

New antifungal targets: bedside to bench

Dominika BoldovjÁková

Background

Life threatening fungal diseases exceed the annual worldwide mortality rates for tuberculosis, malaria or breast cancer. These diseases are present locally as well as globally, however, their impact is commonly overlooked. Invasive forms of disease are difficult to diagnose with limited therapeutic options. In an era of drug resistant infections, comprehensive assessment of new drug targets is crucial.

The fungal cell wall is essential for survival, underlying the hypothesis that enzymes synthesising this complex carbohydrate network are potential antifungal drug targets. *Aspergillus fumigatus* (*Af*) is one of three main genera causing human disease and this ASRS project contributes to the genetic validation of a putative cell wall target. *AfGna1* participates in the sequential conversion of glucose (Glc) into the chitin building block, UDP-*N*-acetylglucosamine (UDP-GlcNAc), a vital component of the cell wall.

Methods

In vitro and *ex vivo* experiments were performed using three *A. fumigatus* strains where the gene encoding Gna1 was (a) present, (b) knocked out (*gna1Δ*) and (c) knocked in. A microdilution checkerboard assay was constructed to assess the interplay of Glc and GlcNAc on *A. fumigatus* viability across simulated physiological concentrations.

Results

In vitro growth of *gna1Δ* is abolished in the presence of Glc (50 mM) but partially overcome with exogenous GlcNAc (50 mM). A heat map from the microdilution assay shows *gna1Δ* is fungistatic with abnormal pigmentation compared to the control strains under simulated physiological sugar concentrations. Synergistic antifungal activity was observed by combining *Afgna1Δ* with caspofungin suggesting gene loss correlates with increased susceptibility to cell wall stressors. Inhibiting cell wall synthesis by two different mechanisms could reduce resistance developing. Initial findings in an *ex vivo* lung model showed *gna1Δ* spores failed to germinate.

Conclusion

The genetic studies show promising results but further *in vivo* genetic and chemical validation is required. *AfGna1* may be a promising target for ultimately developing a new class of antifungals.

Supervisors: Dr. Deborah Lockhart

Telemedicine: Patients' perspectives in the Aberdeen Royal Infirmary Gastroenterology out-patient setting

Philip Cannon

Background

Telemedicine describes a method of delivering medical education and healthcare services from one geographical location to another utilising technology. NHS Scotland is currently implementing various telemedicine-based initiatives but to date none of these have resulted in telemedicine becoming the norm for secondary care outpatient clinic appointments. This pilot study aimed to establish the travel involved in attending an outpatient appointment and explore patients' attitudes to alternatives to attending a traditional Gastroenterology outpatient appointment at Aberdeen Royal Infirmary (ARI).

Methods

A questionnaire was devised capturing the distance and method of travel, the patient's perception of cost, including if leave from work had been taken, along with categorical questions asking the patients to rank various options of alternative consultation types. The questionnaire was distributed by the reception staff of the Gastroenterology outpatient department to patients over a 4-week period (7/6/17- 5/7/17).

Results

572 patients completed the questionnaire. The majority (70.5%) travelled by car with an average round trip of 42 miles (0.5-566 miles), estimated the direct costs to attend clinic at an average of £11 (£0-£365), 35% of them had to take either paid or unpaid leave to attend and 78.6% agreed or strongly agreed that the clinic was accessible. Overall patients predominately preferred to be seen face to face in ARI in most situations, the exception being if they had test results which were ok.

Conclusion

Despite significant travel and inconvenience the majority of patients seemed satisfied with their experience of attending clinic. Our findings have confirmed obstacles such as patient preference for face-to-face conversations, their self-perceived lack of IT skills and lack of access to IT systems. With ongoing improvement in Digital Infrastructure and the penetration of technologies to other areas of patients' lives, further research will establish how telemedicine could best complement the delivery of secondary care outpatient services across Scotland and indeed further afield.

Supervisors: Dr. John Thomson

Maternal dietary fatty acid intake, body fatness, and *in vitro* fertilisation (IVF) outcomes

Bernadine Chua

Background

Body fatness and fat distribution are associated with reproductive function, however little is known about the relationship between maternal dietary fatty acid intake and IVF outcomes. Establishing this relationship would help provide advice for women undergoing IVF treatment and improve success rates. This study aimed to ascertain the association between maternal dietary fatty acid intake and the outcomes of IVF treatment.

Methods

Following ethical consent, a prospective cohort study of 503 women consecutively enrolled while undergoing IVF treatment at the Aberdeen Reproduction unit was carried out. Dietary fatty acid intake was calculated as a percentage of total energy intake based on a self-administered food-frequency questionnaire. Classes of fatty acid intake and individual fatty acids intake were expressed as a percentage of total fat. Plasma and follicular fluid was collected during egg recovery and analysed for fatty acid composition. Linear regression was used to assess the relationship between plasma and follicular fluid composition. Binomial logistic regression tested the association between fatty acid intake and the outcomes of; embryo fertilisation, viable pregnancy and live birth, measured per fresh cycle of IVF or intracytoplasmic sperm injection (ICSI).

Results

The odds of a successful IVF treatment decreased with increased maternal dietary fatty acid intake for some of the fertility related outcomes; viable pregnancy [odds ratio (95% confidence interval), p value] = [0.92 (0.87-0.98), p=0.009] and live birth [0.90 (0.845-0.975), p=0.008]. However, no association was found between dietary fat proportions and embryo fertilisation.

Conclusion

These findings suggest that a high maternal dietary fatty acid intake is associated with poorer outcome of IVF treatment. In women likely to have a successful IVF pregnancy, dietary fatty acid intake was lower. There was no evidence that fat classes or individual fatty acids influenced treatment outcomes but more research is needed to explore how this may be affected by adipose tissue mass.

Supervisors: Professor Paul Haggarty, Professor Siladitya Bhattacharya

Can telemedicine play a role in the delivery of Gastroenterology out-patient services in Aberdeen Royal Infirmary?

Craig Fraser

Background

Telemedicine is defined by the use of information and communication technology to support or enhance the provision of health services at a distance. Reports from the North East of Scotland have demonstrated local telemedicine networks are feasible and beneficial in terms of access to services and cost-effectiveness. It is unknown what role telemedicine could play in the delivery of the Gastroenterology out-patient services at Aberdeen Royal Infirmary.

Methods

A cross-sectional survey was designed to evaluate clinician perspectives regarding the introduction of telemedicine to facilitate the Gastroenterology out-patient service at the Aberdeen Royal Infirmary. For each consultation between 14/6/17 and 7/7/17 clinicians were asked to consider whether the appointment could have been provided in a different format such as: telephone consultation, video consultation, community clinic, remote monitoring or another unspecified method. Patients across all Gastroenterology sub-specialties including Liver, General and Inflammatory Bowel Disease (IBD) were included. Patients attending for treatment clinic consultations were excluded from the study.

Results

Over the study period 88 questionnaires were offered, with 65 returned (74%), equating to a total evaluation of 438 patient consultations. Of these the clinicians indicated 185 (42%) consultations were suitable for an alternative method of consultation. For all patient types, telephone consultation was deemed to be the most suitable alternative of appointment provision. 100 (58.5%) IBD patient consultations could have been seen differently, whereas 71 (41.5%) required an in-person consultation. Clinicians reported the majority of Liver disease and General Gastroenterology out-patient consultations should have been seen in-person.

Conclusion

A cohort of patients within the Gastroenterology service at ARI could be seen by alternative methods utilising telemedicine. Future studies should consider the feasibility, cost and acceptability of the introduction of telemedicine in the delivery of out-patient services from patient and clinician perspectives.

Supervisors: Dr. John Thomson

The Central Vein Sign relationship to the blood-brain barrier in multiple sclerosis

Ioannis Georgiou

Background

Multiple Sclerosis (MS) is an autoimmune disorder of the central nervous system. NHS Grampian has the highest prevalence of MS worldwide. The diagnosis of MS is based on a combination of clinical symptoms and magnetic resonance imaging (MRI) of white matter lesions within the central nervous system. The presence of central veins within white matter lesions with MRI are characteristic of this condition. As the Central Vein Sign (CVS) shows promise as a diagnostic marker of MS, we aimed to review the literature of the pathology between the peri-venous demyelination and the effects MS has on the blood brain barrier (BBB) leading to this manifestation.

Methods

Using PubMed, JAMA-network and Ovid Medline a literature review was carried out. The keywords used to search were: "Central vein sign", "Multiple Sclerosis", "VEGF", "interleukin-1", "Shear stress", "Blood brain barrier", "vein", "transmigration". Articles were selected based on the relevance of their abstracts and the overall aim of this paper.

Results

The literature review identified 62 papers for analysis. The literature supports that BBB of veins is more susceptible to inflammation than arteries because of shear stress and transmigration. Our findings highlight that VEGF and interleukin-1 proteins, are principal components in the pathogenesis. This is further highlighted by the utilisation of String and Cytoscape interaction and functionality analysis, which established the relationship between VEGF and interleukin-1 in the pathogenesis of MS and BBB breakdown.

Conclusion

Our literature review ascertains that veins within the BBB are more susceptible to inflammation compared to arteries because of the heterogeneity of the BBB's structure. Significant proteins in BBB breakdown are interleukin-1 and VEGF. Altogether, these factors unite the existence of the CVS on MRI with the effects of MS on the BBB. Therefore, these factors could potentially help with diagnosis, treatment and prognosis of MS patients.

Supervisors: Dr. Stavroula L Kastora, Professor Alison Murray

Cost of routine TSH testing in fertility clinics

Abstract Only Presentation

Nayl Gilani

Background

Current NICE guidance (CG156) does not recommend routine testing of thyroid function in fertility clinics in those who are having regular periods and have no symptoms suggestive of hypothyroidism. However, pre-conception thyroid stimulating hormone (TSH) testing and optimisation of thyroid status (TSH<2.5mU/L) prior to *in vitro* fertilisation/ intracytoplasmic sperm injection leads to improved live birth rate and reduced miscarriage rates. The cost implications of carrying out routine TSH testing is not known. Therefore, the primary outcome of this study was to determine extra cost per patient, due to routine TSH testing in 2016 at the Aberdeen Fertility Centre.

Methods

All new appointments in the fertility clinic during 2016 were identified through NHS patient management system. The inclusion criteria included a first fertility clinic appointment and at least one TSH test available within 12 months. Clinical data was retrieved from Trakcare® Electronic Medical Record System and patient records. Costs for serum TSH, thyroid peroxidase antibody and an appointment at the clinic were obtained from the Department of Health reference costs database and the total cost for the clinic for the year was determined.

Results

621 appointments were identified of which 511 cases met the inclusion criteria. The total cost of TSH screening in the fertility clinic in 2016 was £5506, a cost of £10.77 per patient.

Conclusion

This is the first study investigating the cost of TSH testing in a fertility clinic. Whether testing and treatment will lead to improvement in clinical outcomes remains to be proven. Due to the association between the risk of miscarriage and TPO antibodies, routine thyroid function testing and treatment with thyroxine in woman pre-conception is warranted. We propose a randomized control trial, exploring the cost effectiveness of TSH screening.

Supervisors: Dr. Abha Maheshwari

Oral Health Behaviours and Oral Health-Related Quality of Life (OHRQoL) in 18 – 25 year old young adults

Owens Iguodala

Background

“Young adult” is a flexible term used to describe the time period between adolescence and adulthood. As this term is not defined by age in dental literature, oral health of this group is poorly investigated and reported. Considering that many habits formed in this period tend to persist in later life and have both short and long-term effects on oral and general health and wellbeing, this review aimed to understand current oral health conditions and their relationship to oral health behaviours and quality of life in young adults, defining this group as individuals aged between 18 and 25 years old.

Methods

A systematic literature review of papers reporting specifically on oral health behaviours (toothbrushing, flossing and use of dental services) and oral health related quality of life (OHRQoL) in young adults aged 18 to 25 years old was conducted. Relevant papers were selected from four electronic databases (MEDLINE, EMBASE, Web of Science and Scopus) using strict inclusion and exclusion criteria.

Results

This review highlights that whilst using this strict criteria, there is a severe shortage of good quality studies looking at this age group as many had small sample sizes, did not include the full age range or were conducted in specific settings (e.g. universities). Furthermore, there was great disparity in the way many oral health behaviour outcomes were measured and recorded, making it difficult to summarise data quantitatively.

Conclusion

This review recommends reaching a consensus with regards to the definition of “young adult” within the context of dental literature and the standardisation of the way oral health behaviour outcomes are measured and reported.

Supervisors: Dr. Ekta Gupta

Making the most of the Aberdeen Birth Cohorts' (ABC 1921, 1936, 1950) – A systematic review of how the data has been utilised in research

Ashan Jayasundera

Background

Cohort studies are employed to assess the aetiology of conditions and their progression in a group of people over a period of time. In Aberdeen, UK, there are three such cohorts: The Aberdeen Birth Cohorts (ABC) 1921, 1936 and the 1950s. They have provided invaluable information from cognitive scoring, to birth weights allowing analysis of health relationships over a longitudinal period of time. The aims of this study were to: Identify the studies that had been done; describe how the data were used in the studies; and determine the most effective way to display this information.

Methods

To determine how data were used, a researcher focus group was arranged to identify relevant information (e.g. outcomes, exposures) to be extracted, alongside baseline information (authors, publication year) from each paper. Data extraction occurred via Excel. Keywords were identified to initiate the search, originating from a list of publications on the ABC website. Finalised keywords were used to perform searches across databases (MEDLINE, EMBASE, Web of Science & NHS Economic Evaluation Database). Following this, resultant publications were screened, before incorporation into the Excel database alongside relevant extracted information.

Results

623 publications were located from the search prior to screening. Removal of duplicates and irrelevant papers reduced this to 130. 37% was from the 1950s cohort, 1936: 36%, 1921: 21%, with remaining papers using multiple cohorts. From 1999-2004, 77% of the publications utilised the 1921 cohort. From 2005-2010, the 1950s cohort produced 61%. From 2010-present, the 1936 cohort contributed the most with 57%. Approximately 40% of the publications focused on mental health and 15% of papers linked data to other health records.

Conclusion

Aberdeen Birth Cohorts have been a well utilised resource but there is much more potential through data linkage and in health domains beyond mental health.

Supervisors: Professor Corrinna Black, Lynn Robertson

Incidence of dementia in Parkinson's Disease in the PINE study

Quasir Khan

Background

There are few data on the incidence rate of dementia in patients with Parkinson's Disease (PD) compared to controls in representative samples.

Methods

The PINE study recruited 203 incident Parkinsonian's patients along with 260 age-gender matched community based controls in Aberdeen. They gave consent for standardized annual life-long follow up. Their primary, secondary care and research records were reviewed to identify those who developed dementia defined by (1) DSM-IV based clinical diagnosis by an expert neurologist/psychiatrist and (2) the Movement Disorder Society (MDS) research criteria for PD dementia (applicable to 194 patients). Incidence rates were calculated along with the hazard ratio for dementia in patients vs controls using Cox regression. MDS criteria and clinically diagnoses were compared.

Results

89 patients (49 male, 40 female) were diagnosed with dementia compared to 33 (13 male, 20 female) in controls over a median follow-up of about 8 years. Mean age at the time of diagnosis with dementia was 80.2 years in patients compared to 85.4 years in controls. The hazard ratio was 6.4 for dementia in patients vs controls adjusted for age and gender. The MDS criteria was highly specific (88%, 95% CI 81-93%) but not sensitive (66%, 95%CI 55-75%).

Conclusion

People with Parkinson's are 6.4 times more likely to develop dementia over controls. Research criteria underestimate true dementia rates.

Supervisors: Dr Carol Counsell

Winter excess in hospital admissions, in-patient mortality, and complications in stroke: A Thailand National Database Study

Nicole Lorking

Background

There are limited data around winter excess in stroke within tropical climates, and particularly whether such a phenomenon exists.

Methods

In a cohort (n=594,681) of prospectively hospitalised stroke patients from Thailand, we examined the presence or absence of a winter excess (Winter: November-February; Hot season: March-June; Rainy season: July-October) in number of admissions, in-hospital mortality, and prolonged hospitalisation (between 1st October 2003 and 31st January 2013). Data were collected on comorbidities and post-stroke complications. Rates of incident stroke by month and season were plotted. A winter excess index was calculated for all variables. Seasonal differences in outcomes were examined using chi square tests.

Results

594,681 stroke patients (mean[SD] age = 64[14.5]) were included in this study (306,154 ischaemic; 195,392 haemorrhagic; 93,135 undetermined). Rates of incident stroke increased across study follow up (n (rate/100,000) during winter, hot, and rainy seasons respectively = 16387(31.5), 13684(26.31), 14967(28.78) in 2004 and 28862(53.18), 27678(51.00), and 29260(53.91) in 2012). There was a winter excess in mortality during hospitalisation (+22.6%) and in prolonged hospitalisation (+12.0%) compared to non-winter months (all patients). Older patients (>75 years) with haemorrhagic stroke primarily contribute to the winter excess of stroke admissions (+36.1% for males and +33.8% for females). Patients who died during winter admission (77,426(13%)), were more likely to be male (54.9%) with haemorrhagic stroke (66.8%) (respective winter excess indexes = +24.9% and +26.9%). Dyslipidaemias, arrhythmias, anaemia, and alcohol related disorders were more prevalent (respective winter excess indexes = +15.8%, +15.8%, +12.0%, +11.7%) in these patients, as were post-stroke complications of pneumonia, respiratory failure, sepsis, convulsions, myocardial infarction, and shock (respective winter excess indexes = +18.4%, 18.5%, 11.2%, 9.9%, 12.7%, 11.7%).

Conclusion

We are the first study to show the presence of a winter excess in stroke incidence, acute mortality, and length of hospitalisation in stroke patients from Thailand.

Supervisors: Professor Phyto Myint, Dr. Adrian Wood

Inter-pregnancy BMI change and the risk of preeclampsia (PE) and small for gestational age (SGA) babies: Analysis of the first two pregnancies in women from three European countries

Dylan McClurg

Background

Although maternal weight gain is strongly associated with the risk of adverse pregnancy outcomes, research on the effect of inter-pregnancy weight change on the risk of pregnancy complications is limited.

Methods

A cohort study of 551,592 women from three European datasets (Finland, Malta, and Aberdeen) was undertaken. Inter-pregnancy weight change was calculated from the difference between BMI recorded in the first two pregnancies. Weight change was characterised as an increase or decrease of ≥ 2 BMI units between pregnancies and compared with weight-stable women who remained within 2 units. Univariate and multivariate logistic regression analyses were employed to examine the associations.

Results

The adjusted odds ratio (AOR) for PE was 1.22 (95% confidence interval 1.09-1.37) for inter-pregnancy weight gain when compared to weight-stable women. A decrease in BMI showed no significant reduction in risk of PE (AOR 1.07 (0.87-1.32)). In contrast, increase of >2 BMI units suggested a protective role against SGA (AOR 0.83(0.73-0.95). Reduced BMI resulted in an increased risk of SGA (OR 1.18(1.04-1.34). However, this relationship was not evident once adjusted for confounding factors (AOR 1.03(0.85-1.23). SGA and PE in first pregnancy were found to greatly increase the risk of recurrence in the second pregnancy (AOR 15.24 (13.80-16.84) & AOR 2.69 (2.11-3.44), respectively). Having either SGA or PE during second pregnancy resulted in an increased risk of the other occurring; PE risk AOR 3.99 (3.27-4.87) and SGA AOR 4.10 (3.40-4.95).

Conclusion

We show that a weight gain >2 BMI units was associated with an increased risk of PE but reduced the risk of SGA. While weight loss of 2 units did not affect PE risk, it did increase the risk of SGA on unadjusted analyses. Additionally, women who have had previous PE or SGA have an increased risk of recurrence.

Supervisors: Dr. Sohinee Bhattacharya

Determinants of Oral Health-Related Quality of Life in the institutionalised elderly: A systematic review

Mhairi McGowan

Background

Oral Health-Related Quality of Life (OHRQoL) has become an increasingly popular concept in recent years. As a population that suffers from reduced quality of life and oral health, it is important to assess OHRQoL and its determinants in the ever-growing elderly population, particularly those in care-settings. Whilst there is a growing body of literature in this area, there is no unanimous agreement regarding the determinants of OHRQoL in the institutionalised elderly. Thus, this systematic review aims to identify factors associated with OHRQoL in this population.

Methods

Electronic databases (Medline, Scopus and Web of Science) were systematically searched for papers written in English between 1950 and July 2017 that fulfilled the predefined inclusion criteria as follows; patients had to be institutionalised and over 60 years old, and OHRQoL had to be linked to any given determinant.

Results

Excluding duplicates, 7301 papers were identified. From these, 19 were included in this review. Seven studies reported that patients' subjective dental and/or general health were significant determinants of OHRQoL. Clinical oral health parameters, including caries experience, periodontal disease and use of prosthetics, were not consistently related to OHRQoL. Although edentulism was not strongly correlated with OHRQoL, a functional dentition was a determinant in three studies. Both studies which assessed nutritional status and masticatory function found these to be important determinants. Socioeconomic or sociodemographic factors were not determinants in this population.

Conclusion

Patients' perception of their health was a stronger determinant of OHRQoL than clinical measures, highlighting the importance of an individual's own values, comfort and happiness with regards to health. Research should be focused on the factors associated with subjective oral health and ways in which to enhance this.

Supervisors: Dr. Ekta Gupta

High anticholinergic burden in middle-aged women is associated with recurrent falls in later life

Samuel R Neal

Background

Falls are a significant source of morbidity and mortality globally. Anticholinergic burden (ACB) is a risk factor for falls in the elderly. However, whether ACB exposure in middle age predicts falls and fractures in later life has not been examined.

Methods

Women who attended all health visits of the Aberdeen Prospective Osteoporosis Screening Study (APOSS) were followed up for a maximum of 13.8 years (mean [SD] 11.4 [\pm 1.3] years), totalling 20,957 person years. ACB was calculated based on a written list of current medications at the second health visit between 1997-1999 (study baseline) using the Anticholinergic Cognitive Burden Scale. Outcomes were falls and recurrent falls (≥ 2 falls) during 12 months prior to follow up (2007-2011, mean [SD] age 66.0 [\pm 2.2] years), and incident fractures between baseline and follow up. Logistic regression analyses adjusted for potential confounders, including demographics, comorbidities and history of falls. Outcomes were ascertained by self-reported questionnaires.

Results

A total of 1845 women (mean age [SD] = 54.7 [\pm 2.2] years at baseline) were included. The prevalence of baseline ACB score of 0, 1 and ≥ 2 were 86.6%, 7.6% and 5.8%, respectively. An ACB score ≥ 2 was associated with more than 2-fold increased odds of recurrent falls (adjusted OR 2.20 [1.23-3.94], $p=0.008$) compared to no ACB. Six participants with ACB reported fracture, precluding further

Conclusion

For the first time, we describe the link between exposure to high ACB in middle-aged women and recurrent falls in later life. In the absence of trial data, it is advisable that attempts should be made to reduce the anticholinergic burden in middle age.

Supervisors: Dr. Adrian D Wood, Professor Phyo K Myint

Myocardial infarction after stroke: time-dependent predictive co-morbid factors, incidence, and mortality

Tiberiu Pana

Background

Ischaemic heart disease and stroke are the two leading causes of mortality worldwide. However, there is limited information regarding their association. We have thus aimed to describe the acute myocardial infarction (MI) incidence after stroke, determine the biological covariates and comorbidities predicting this event, and examine excess mortality in such cases.

Methods

This observational study included 11,422 prospectively identified patients aged ≥ 18 years admitted to a tertiary referral centre in the East of England, UK (January 2003-December 2016) with a diagnosis of stroke. Follow-up data were collected for a minimum of 6 months. Predictive factors (age, sex, stroke type, disability status, biological covariates, and comorbidities) for post-stroke MI, incident event data, and patient mortality were examined.

Results

The mean age (SD) of study patients was 77.3(12.2) years (48% males). Cumulative MI incidence over 10 years of follow-up was 5.23%. Patients with MI in hospital had higher 10-year mortality than those without (65.0% vs. 44.3%). Patients with MI during follow-up were more likely to die (HR(95% CI) = 2.68(2.08-3.44)). Factors associated with MI in hospital were higher CRP ((OR(95% CI) for 10 mg/L change) (1.06(1.03-1.09)), total white cell count ($10 \times 10^9/L$ change) (1.27(1.04-1.54)) and blood glucose (10 mmol/L change) (1.69(1.14-2.50)). Time-updated factors associated with incident MI between discharge and 1 year were older age (HR(95%CI) = 1.04(1.02-1.06)), cancers (1.66(1.06-2.61)), chronic kidney disease (2.15(1.25-3.69)), and recurrent stroke (2.26(1.12-4.55)), and between 1 and 5 years were older age (1.04(1.02-1.06)), dyslipidaemia (1.51(1.02-2.23)), coronary heart disease (1.62(1.12-2.35)), diabetes mellitus (2.04(1.41-2.96)), peripheral vascular disease (2.29(1.34-3.91)) and heart failure (2.40(1.63-3.52)).

Conclusion

Post stroke MI is uncommon but carries a poor prognosis over the long-term. We have identified the risk factors predictive of post-stroke MI over discrete time periods which can be used to target high risk phenotype patients and reduce the risk of future cardiovascular events.

Supervisors: Dr. Adrian D Wood, Professor Phyo K Myint

A novel murine model of conditional BSCL2 knockout in adiponectin-expressing cells: histomorphometric effects on the infra-patellar fat pad of the knee

James Redmore

Background

The infra-patellar fat pad (IPFP) is an intracapsular but extra synovial structure within the knee joint, and has been postulated to contribute to local osteoarthritis (OA) development. The Cre-Recombinase method was utilised to create a novel murine model of Berardinelli-Seip Congenital Lipodystrophy 2 (BSCL2) gene deletion. This was specific to cells expressing adiponectin (Ad), a pro-inflammatory cytokine released almost exclusively from adipose tissue. The aim of this study was to validate this model of selective BSCL2 gene deletion by assessing IPFP size and adiposity in control and knockout mice.

Methods

All mice were male, comprising Ad-Cre;BSCL2^{fl/fl} (cKO, n=7) and a mixture of heterozygous and wildtype;BSCL2^{fl/fl} controls (Ctl, n=11). Left hindlimbs were collected at aged 12 weeks, processed, fixed and embedded in wax. Sequential 5µm sections were cut, before H&E and Safranin-O stains were performed to aid visualisation the IPFP and knee-joint articular cartilage. Zeiss AxioScan Slide Scanner was used to obtain 200x images of stained slides. Zen 2.3 (Blue Edition, 2011) software was used to quantify IPFP size and adiposity using the spline contour and cell count features, respectively. Data analyses were performed using Stata 15, with p≤0.05 indicative of statistical significance.

Results

A statistically significant decrease in IPFP adipocyte number in cKO compared with Ctl (mean reduction 320 cells, p<0.01) was observed. However, there was no difference in IPFP size overall (0.7mm² reduction in cKO compared with Ctl, p=0.99). Visual inspection of extra-articular subcutaneous fat highlighted reductions in cKO samples compared with Ctl.

Conclusion

Adipocyte depletion within the IPFP was confirmed in the Ad-Cre;BSCL2^{fl/fl} model. Mechanistic studies are required to elucidate the role, if any, that the IPFP plays in knee-joint OA pathogenesis, in addition to comparative experimental studies of knee-joint OA development. Models such as the above could be one avenue of exploring this in future years.

Supervisors: Dr. Anke Roelofs, Mrs Alison Richmond, Professor Cosimo De Bari

Can haematology blood tests at time of diagnosis predict response to neo-adjuvant treatment in locally advanced rectal cancer?

Duncan Ritchie

Background

Mortality outcomes in the treatment of locally advanced rectal cancer are reduced by neoadjuvant therapy followed by surgical resection. However, some patients will completely respond to preoperative treatment and show no evidence of neoplasia at the time of operation. Such individuals may not have benefited from the secondary, high risk, procedure. Therefore, predicting the pathological response to preoperative therapy is of significant clinical importance. We aim to examine the predictive value of haematological blood tests at the time of diagnosis on response to neoadjuvant therapy.

Methods

All patients undergoing resection of rectal adenocarcinoma after neoadjuvant therapy in a single centre between 2006 and 2015 were included. Patients were identified from a prospectively collected colorectal cancer pathology database and data were supplemented retrospectively with full blood count at the time of their diagnosis. Specimens resected following neoadjuvant therapy were graded according to pathological response. Follow up were obtained from the national cancer registry. Receiver Operator Characteristic (ROC) curve analysis was used to examine predictive value. Haematological counts were assessed both as individual parameters and as two-parameter ratios.

Results

Of 330 patients included, 71 (21.5%) responded completely to preoperative therapy. 238 patients received chemo-radiotherapy (72.1%) while 63 (19%) received radiotherapy alone and 29 (8.8%) received chemotherapy alone. The marker with the highest area under the curve (AUC) was white cell count (WCC), producing an AUC value of 0.666. The integer value of WCC closest to 1 on ROC curve was 8×10^9 cells/L. Kaplan-Meier survival analysis was also performed; those patients with WCC >8 had poorer survival than those with WCC <8 .

Conclusion

Routinely collected haematology samples at the point of diagnosis can assist in predicting for complete response to neo-adjuvant therapy. These findings could help to assist in risk stratification of patients using routinely collected laboratory tests.

Supervisors: Mr. George Ramsay

Improving access to fracture prevention services in island communities

Natalie Smellie

Background

National Osteoporosis Society clinical standards for Fracture Liaison Services emphasise the importance of identifying and investigating individuals who are at high risk of fracture, to prevent future fragility fractures. Data from patients referred from Shetland to Aberdeen prior to introduction of a mobile bone density scanning (DXA) service indicated they were younger with lower risk of fracture. This project examined if introduction of a mobile DXA service to island communities improved access to care for elderly, often frail patients at high risk of fracture. The fracture risk of patients referred to a mobile service on Shetland and Orkney was compared to pre-mobile data and that of a comparable mainland community with local service access (Moray). Fracture risk was assessed using a fracture risk calculation tool (FRAX).

Methods

Data from DXA scans conducted in Moray between 01/04/16 - 01/07/16, and the mobile service for Shetland and Orkney between 01/04/16 - 31/03/17 were collected. This included bone density, age, gender, and osteoporotic risk factors. Patient's ten-year risk of major osteoporotic and hip fracture was calculated using FRAX.

Results

Patients mean age was 66 in Moray, 67 in Shetland and 69 in Orkney; comparison with pre-mobile data from Shetland indicated mean age increased from 58.5. FRAX scores of referrals had also increased from 12% to 16.4% (major osteoporotic fracture), and 2.8% to 5.1% (hip fracture), and was comparable to Moray. In particular referrals from those with previous fractures and glucocorticoid use increased, from 44% to 70% and 28% to 34.2%, respectively.

Conclusion

Results indicate that introduction of a mobile service to the islands has facilitated identification and assessment of those at high fracture risk, who were previously unable to access DXA services; particularly patients with co-morbidities and prior fractures who struggled to access mainland services. Results from this study have helped support mobile DXA service sustainability.

Supervisors: Dr. Rosemary Hollick, Dr. Alison Black

Association between breast cancer risk and characteristics and the dietary intake of fats and fat soluble vitamins

Maria Soupashi

Background

The recent World Cancer Research report (2017) recognises obesity throughout adulthood as a risk factor for breast cancer. The role of individual dietary fatty acids however, in the initiation and progression of cancer, remains unclear as studies show conflicting results.

Methods

Dietary, clinical and related data from a Scottish cohort of 719 women (538 controls and 181 cases) were utilised in logistic regression to search for associations between breast cancer incidence and the intake of dietary fats (as a percent of total fat) and fat soluble vitamins. The case group consisted of ductal carcinoma *in situ* (DCIS) and invasive ductal carcinoma (IDC) types and controls were also compared to each of them separately. Subgroup analysis was carried out in the IDC group (n = 146) to look for associations with receptor subtype (ER/PR/HER2), triple negative (TN) status, lymphovascular invasion, grade and Nottingham Prognostic Index (NPI).

Results

Intake of arachidonic acid and total long chain omega-6 fatty acids was negatively associated with cancer incidence in all cases ($p=0.021$ and $p=0.023$ respectively) and IDC alone ($p=0.003$ for both). Intake of myristic acid was positively associated with incidence of IDC ($p=0.019$). No associations were found for ER/PR subtypes and lymphovascular invasion. Intake of palmitic acid was associated with an increased likelihood of a HER2 negative tumour ($p=0.044$), while vitamin E showed an opposite association ($p=0.045$). Intake of linoleic acid and total omega-6 fatty acids was associated with increased chances of a TN tumour ($p=0.013$ and $p=0.012$ respectively) and a worse grade ($p=0.041$ and $p=0.043$ respectively) while at the same time decreasing the likelihood of a better NPI score ($p=0.026$ for both). Decreased chances of a good NPI score were also observed for vitamin E intake ($p=0.021$).

Conclusion

A putative role for omega-6 fatty acids is suggested in the progression of breast cancer and the effect seems to be specific to cancer type. Potential mechanisms include free radical and pro – inflammatory eicosanoid production.

Supervisors: Professor Paul Haggarty, Professor Steven Heys



HOTSTART

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The effect of YAP knockout in joint inter-zone progeny on the mature skeleton

Mazen Allam

Background

A key molecular pathway identified in recent years to control cell proliferation and tissue/organ growth is the Hippo pathway. Uncontrolled activity of YAP, a key Hippo pathway transcription co-factor, causes tissue overgrowth due to modulation of stem cell proliferation. YAP is involved in limb development in chondrogenesis. YAP has also been identified as potential target in achieving joint homeostasis after injury. The long term effect of targeting YAP are not yet characterized. Our aim was to complete a phenotypical analyses of the effect of a YAP knockout in joint inter-zone progeny on the skeleton of aged mice.

Methods

Gdf5CreYap^{tdTom} mice (homozygous (HO) and wild type (WT) littermates) in which YAP is knocked out in cells originating from the joint inter-zone (Gdf5 progeny) were aged to a year old and both hind limbs harvested. Histological analysis was conducted on the left legs using Safranin O/Fast Green staining and light microscopy. Radiological imaging was conducted on the right legs using microCT. Computer analysis allowed 3D outcomes to be obtained for bone microarchitecture.

Results

In total, 15 mice (9 female and 6 male) were analysed. At one year no obvious differences in osteophyte formation or cartilage morphology was detected. Overall, radiological analysis showed no difference in cortical, metaphyseal and subchondral bone. However, on subgroup analysis, trabecular thickness was decreased in metaphyseal bone in HO males vs WT males ($p < 0.01$) and increased in subchondral bone of HO females vs WT females ($p = 0.018$).

Conclusion

No deleterious effects on the ageing joint were detected. Further work is needed to determine whether the observed change in bone microarchitecture are directly related to YAP knockout in Gdf5 progeny and whether these are attributable to bone formation or breakdown. The long term consequences of using novel drugs, which target YAP, require careful evaluation to avoid unintended side effects.

Supervisors: Miss Anna Riemen, Dr. Anke Roelofs, Professor Richard Aspden, Professor Cosimo De Bari

Probiotic supplementation for the treatment of behavioural & cognitive symptoms in neurodegenerative disease: A systematic review

Edward Bader

Background

Behavioural & cognitive symptoms are a hallmark of neurodegenerative disease. Recently, the concept of the gut-brain-axis (GBA) has emerged, whereby an individual's gut milieu is able to influence brain functioning via neuronal, hormonal and immunological mechanisms. Interventions, thought to act via the GBA, are now being trialled for neurological disease. This review aimed to assess whether probiotic supplementation is of therapeutic benefit for behavioural & cognitive symptoms in patients with neurodegenerative disease.

Methods

The online MEDLINE database was searched in May 2017 (re-searched October 2017) and any controlled trials reporting the use of probiotic interventions in patients with previously diagnosed neurodegenerative disease, and which reported behavioural or cognitive outcomes, were included. Bibliographies of included studies & papers citing included studies were additionally screened. Data extraction & methodological quality assessment were undertaken in a standardised & bespoke manner. Additionally, a narrative review into the ways probiotics might influence the GBA is also being undertaken.

Results

173 papers were identified, of which 1 met inclusion criteria. 60 patients were included in total (mean age 79.8 years). All patients were diagnosed with Alzheimer's Disease & residents in care homes. The trial was a double-blind, randomised controlled trial. Patients were randomised to either daily supplementation with probiotic-containing milk or normal milk. Mini-mental state examination (MMSE) scores (out of 30) were recorded in all participants before & after intervention. Patients receiving probiotic supplementation demonstrated an improvement in mean MMSE score (baseline: 8.67, end-of-trial: 10.57) compared to controls, who demonstrated a reduction in MMSE score (baseline: 8.47, end-of-trial: 8.00) ($p < 0.001$).

Conclusion

Probiotic supplementation in patients with Alzheimer's Disease demonstrates promising results, with improvement in cognitive function. Given the small number of studies & participants, further trials are warranted to determine the efficacy of probiotic supplementation & whether this benefit is replicated in other neurodegenerative diseases.

Supervisors: Professor Alexandra Johnstone. Professor Phyo Myint

Efficacy of cryoprecipitate versus fibrinogen concentrate in clot formation and stability: Implications for treatment of trauma induced coagulopathy

Fiona Craigen

Background

Fibrinogen is a major factor in forming a stable clot and is more sensitive to depletion post-trauma than other clotting factors. The aims for this project were to determine the optimal fibrinogen concentration to achieve adequate clot stability, and to compare the effects of cryoprecipitate and fibrinogen concentrate on clot formation, firmness and stability in plasma from healthy volunteers and trauma patients.

Methods

Fibrinogen depleted plasma was used to determine the appropriate concentration of fibrinogen added to samples which formed a stable clot. Absorbance based assays were used to monitor the clot formation and lysis over a 4 hour period. This allowed for the calculation of maximum absorbance of the clot and 50% lysis time. ROTEM allowed quantitative analysis of changes in viscoelastic properties of the clot. We also performed these methods using trauma patient samples with the added fibrinogen source at different concentrations.

Results

The plasma clot lysis assay demonstrated that absorbance of the clot at 405nm increased in a linear trend with increased fibrinogen concentration when the cryoprecipitate source was added to fibrinogen depleted plasma. This trend was also seen for the fibrinogen concentrate but there was no significant difference between 2.0 and 3.0mg/ml of fibrinogen. From the ROTEM data, it was seen that both the cryoprecipitate and the concentrate resulted in increased MCF (maximum clot firmness) with increased fibrinogen concentration. However, in all cases 3.0mg/ml consistently produced the highest MCF value between 20 and 30mm which was significantly higher than the other measured concentrations.

Conclusion

Our findings confirm that 3.0mg/ml fibrinogen is the optimum concentration to consistently achieve formation of a stable clot. We also found that in both healthy volunteers and trauma patients, cryoprecipitate was a more effective fibrinogen source compared to the fibrinogen concentrate.

Supervisors: Dr. Claire S Whyte, Dr. Nicola J Mutch

Characterisation of serotonergic cells in the brain

Letizia Delle Vedove

Background

Serotonin (5-HT) is one of the major neurotransmitters in the brain and its activity was seen to have a great importance in the regulation of energy balance. The localisation of 5-HT receptors within the brain is important to understand the mechanisms underlying the regulation of body weight and food intake and therefore being able to design new therapies to overcome obesity. The aim of the project was to detect specific mRNA fluorescence *in situ* hybridisation (FISH) probes for 5-HT_{2C} and 5-HT_{1B} receptors in brain tissue.

Methods

For this experiment, the brain tissues of HTR2cC:Rosa26YFP and HTR2cLoxTB (knock out (KO)) mice were used. The fresh frozen mice brains were sectioned in series of 12 µm using a cryostat, mounted on super-frost microscope slides and kept at -80°C until used. The tissue was then fixed and pre-treated to prevent mRNA degradation, and incubated overnight with the different probes at 60°C. The mRNA probe was then detected using the specific antibody Anti-DIG-POD and the signal was amplified using the Tyramide Signal Amplification kit. The slices were stained with 4',6-diamidino-2-phenylindole dihydrochloride (DAPI) for nucleus detection and analysed at the fluorescence microscope.

Results

The tissue hybridised with the probe for 5-HT_{1B} receptor detection showed a good level of labelling in the expected brain regions. The first probe designed for 5-HT_{2C} receptor detection showed, on the other hand, some hybridisation signal in wildtype and reporter line tissue, and a weak, unexpected fluorescence signal in the KO. The second probe designed for 5-HT_{2C} receptor showed a greater level of specificity.

Conclusion

FISH and mRNA detection requires the design of highly specific probes. If such specificity is low, then the probe may give unexpected results that can be misinterpreted. The results obtained with this study will help to characterise the expression pattern for 5-HT_{2C} and 5-HT_{1B} receptors.

Supervisors: Dr. Pablo Blanco Martinez de Morentin

The major melatonin metabolite 6-hydroxymelatonin sulphate increases during pregnancy, associated with decreased oxidative stress

Haroon Ejaz

Background

Melatonin is known to have antioxidant properties and melatonin synthesising enzymes are present within placental tissue. Whether endogenous melatonin protects against oxidative stress during normal pregnancy is unclear. We measured circulating levels of serum 6-hydroxymelatonin sulphate, the major melatonin metabolite, in pregnant women during each trimester of pregnancy and compared this to non-pregnant women. We also investigated the relationship between melatonin and lipid peroxidation as a measure of oxidative stress.

Methods

The study was designed as a prospective observational pilot longitudinal cohort study using healthy primigravid pregnant women and healthy non-pregnant women of child-bearing age. Thirty healthy pregnant women were recruited during the first trimester of pregnancy and followed up to delivery, along with 30 healthy non-pregnant women as controls. Blood samples were taken from pregnant women in each trimester, and a single blood sample from the non-pregnant women was also obtained. Levels of serum 6-hydroxymelatonin sulphate and 8-iso-prostaglandin F_{2a} as a measure of lipid peroxide were determined using commercially available immunoassays.

Results

Median [range] levels of 6-hydroxymelatonin sulphate in pregnant women were 5-fold higher in the first trimester than those in non-pregnant women (86.1 [35.0-224.1] pg/ml compared to 16.5 [4.8-42.3] pg/ml, $p < 0.0001$). Levels increased markedly throughout pregnancy and were up to 100-fold higher than non-pregnant controls by the third trimester (392.2 [100.3-1981.3], $p < 0.0001$). Levels of 8-iso-prostaglandin F_{2a} in the first trimester were not different to non-pregnant controls (1490.0 [291.0-2281.8] pg/ml compared to 1004.5 [246.8-2598.5] pg/ml) but decreased as pregnancy progressed (978.6 [556.9-2662.6] pg/ml in the third trimester, $p = 0.01$).

Conclusion

Circulating melatonin production increased significantly during normal pregnancy, associated with smaller decreases in lipid peroxidation. The increased melatonin is likely to be placental; however the extent to which placental melatonin protects against oxidative stress is unclear with more research required.

Supervisors: Professor Helen Galley, Dr. Andrea Woolner

Electric field stimulation overcomes aggrecan inhibition of neurite growth

Maria Lipodat

Background

Spinal cord injury (SCI) has devastating consequences for the patient's quality of life. Currently there is no cure for SCI, however a combined electrical, physical and pharmacological treatment approach is under development. The purpose of this therapy is to overcome the physical and inhibitory chemical barriers at the injury site that prevent nerve regeneration. The inhibitory molecule studied in this project was the proteoglycan core protein aggrecan, which accumulates in the extracellular matrix at the injury site. The aim was to determine the ability of an applied electric field (EF) to rescue nerve growth inhibition by aggrecan.

Methods

Xenopus laevis embryos were reared in 0.1xMMR solution until stage 20-22. The neural tubes of 2-3 embryos were dissected out, disaggregated in divalent-free Steinberg's solution, re-suspended in culture medium and plated in custom made chambers for 150 mV/mm exposure and time lapse observation. Data were collected from photographs of neurons taken hourly for 3 hours. The hourly change in neurite length and the direction of growth cone movement were recorded.

Results

The speed of neurite growth with an EF (30.6 $\mu\text{m}/\text{h}$, $n=158$) was significantly greater than without an EF (21.1 $\mu\text{m}/\text{h}$, $n=141$) ($p=0.000015$). In the presence of aggrecan the speed of neurite growth (15.3 $\mu\text{m}/\text{h}$, $n=33$) was slower than in without it (30.6 $\mu\text{m}/\text{h}$, $n=158$) and the number of growing neurites was reduced. Under conditions of aggrecan combined with an EF the speed of growth (31.3 $\mu\text{m}/\text{h}$, $n=112$) was twice as fast as with aggrecan but no EF (15.3 $\mu\text{m}/\text{h}$, $n=33$; $p=0.000081$). The mean angle of growth cone turning during 3h for no EF was 4 deg but growth cones were deflected toward the cathode by -24 deg ($p = 0.000000091$), which is similar to the extent of cathodal turning in the EF when aggrecan was present (-17 deg).

Conclusion

The EF increased the rate of neurite growth and directed growth toward the cathode in all conditions, which implies that an EF can rescue neurites from aggrecan inhibited neurite growth. These findings can be applied to the development of an electrotherapy to treat SCI.

Supervisors: Dr. Ann Rajnicek

CLEC12A inhibits inflammation and neutrophil extracellular trap formation in a context of murine collagen antibody induced rheumatoid arthritis

Guillaume P Mignot

Background

C-type lectin-like receptors (CTLRs) are a family of transmembrane receptors involved in inflammation modulation. CLEC12A is an inhibitory CTLR and is expressed mainly on myeloid cells, including neutrophils. Neutrophils play an important role in the pathogenesis of rheumatoid arthritis (RA) by participating in inflammation and releasing neutrophil extracellular traps (NETs). These are believed to provide a source of citrullinated autoantigens, fuelling the autoimmune process. CLEC12A was shown to inhibit inflammation in a context of murine RA, via inhibition of the signalling carried out through activatory CTLRs. It was also established that monosodium urate crystals (MSU) were a ligand for CLEC12A. However, its precise role, structure and cellular location remain to be elucidated. So far, all therapeutic approaches in rheumatoid arthritis (RA) focus on inhibiting directly inflammation. Therefore, the design of pharmacological compounds able to enhance signalling through CLEC12A could potentially offer a novel line of attack in RA. Objectives: determine the role of CLEC12A in modulating inflammation and NET formation in a murine model of RA and identifying its endogenous ligand.

Methods

Characterisation of the activation state of CLEC12a deficient neutrophils from CAIA mice was analysed by flow cytometry. NET release by thioglycollate-elicited CLEC12a deficient and WT neutrophils was quantified by Sytox Green staining and visualised by fluorescent microscopy. Fc-fusion proteins and BWZ.36 reporter cells were used for CLEC12a ligand screening.

Results

CLEC12A inhibits inflammation in response to MSU stimulation. NET formation and neutrophils from the arthritic joint of CLEC12A knockout mice exhibit increased expression of activation markers CLEC12A's ligand is predominantly found on endothelial cells.

Conclusion

CLEC12A may provide a novel target in the treatment of RA. The fact it only acts on activated neutrophils may give CLEC12A inhibitors greater selectivity and a better side effect profile than the drugs presently used.

Supervisors: Lauren Whitehead

The inclusion/exclusion of Nonidet P-40 detergent to brain lysates affects the levels of amyloid and tau proteins detectable in subsequent brain fractions

Thomas KM Ng

Background

Amyloid (A β) plaques and tau containing neurofibrillary tangles are the neuropathological hallmarks of Alzheimer's Disease (AD). Both A β and tau exist in a variety of molecular structures which vary in toxic potential and solubility. The order of solubility progresses from cytoplasmic/detergent soluble species as the least aggregated, to membrane/SDS soluble species and subsequently, detergent insoluble aggregates. Despite the need to ensure the measurements of defined pathological species for diagnosis alongside causative and therapeutic investigation, intra-lab protocols for multi-step tissue fractionation differ. A key variation in these protocols is the inclusion or exclusion of detergents within the initial tissue homogenisation.

Methods

Brain samples (7 non-AD cases and 7 AD cases) were obtained via the Brains for Dementia initiative from the MRC London Neurodegenerative Diseases Brain Bank and Oxford Brain Bank and homogenised with or without the inclusion of NP-40 detergent. Primary antibodies including AT8 (phospho-tau) and MOAB-2 (A β) were used in immunoblots to investigate 3 of the fractions extracted from brain homogenates: the "crude" soluble fraction, containing both the soluble and dispersible fractions, the membrane associated fraction and the ultrasoluble fraction extracted via ultracentrifugation. Graphpad Prism was used to analyse data for statistical significance.

Results

In groups where detergent was excluded, the presence of amyloid and tau proteins was increased in soluble and ultrasoluble fractions compared to groups where detergent was included. We suggest that this may be accounted for by increased cellular lysis in detergent groups which may increase the presence of non-relevant proteins in the homogenate.

Conclusion

Our findings suggest that NP-40 detergent affects the sensitivity of immunoblot assays and leads to differing levels of detectable amyloid and tau within brain fractions. For optimal detection of amyloid and tau isoforms, depending upon the brain fraction, researchers must consider whether the inclusion of detergent is appropriate for their protocol.

Supervisors: Dr. David Koss

Deciphering the role of regulatory CD4 T cells in oral and oropharyngeal cancer: a systematic review

Caoimhin O'Higgins

Background

Recruiting regulatory CD4 T cells (Tregs) into the tumour microenvironment is an important tumour escape mechanism. Selective depletion of Tregs has proven successful in enhancing anti-tumour immunity and therapeutic efficacy in multiple tumour types. However, the role of Tregs in oral/oropharyngeal cancers is unclear with conflicting evidence regarding the effect of these suppressive cells on tumour prognosis. In this study, we sought to review the role of Tregs in oral/oropharyngeal cancer with the aim of deciphering the controversy regarding their effect on tumour progression and prognosis.

Methods

A systematic review of the literature pertaining to the role of Tregs in oral/oropharyngeal cancer was performed using Scopus, EMBASE and PubMed. Forty-seven records were deemed eligible and data describing methodology of Treg detection, tumour type and association with prognosis were extracted.

Results

Transcriptional factor forkhead box P3 (Foxp3) was the most commonly used marker for Treg identification (81% of studies). Sixteen studies were carried out using peripheral blood samples, while samples from the tumour site were analysed in 20 studies. Eleven studies found that an increase in Tregs in the tumour microenvironment and/or peripheral blood was found to be associated with poorer prognosis. This is attributed to the suppression of immune responses and the consequent tumour progression. Conversely, eight studies showed that an increase in Tregs in peripheral blood and/or tumor microenvironment is related to a favourable prognosis, particularly in the presence of human papilloma virus.

Conclusion

This review underlines the importance of host immunity in the behaviour of oral/oropharyngeal cancer. Furthermore, we report an apparent lack of clarity regarding the true role Tregs play in oral/oropharyngeal cancer progression which could be attributed to inconsistent detection techniques of Tregs. Our results therefore highlight the need for clearer methodologies and more robust phenotyping when identifying Tregs.

Supervisors: Dr. Rasha Abu Eid

The role of neuro-inflammation in Alzheimer's Disease progression

Kerri Palmer

Background

Alzheimer's Disease (AD) is the most common form of dementia; its pathological hallmarks include extracellular amyloid ($A\beta$) plaques and neurofibrillary tau tangles. Neuro-inflammation may have important functions in AD pathology but its exact contribution remains unknown. Here we investigated the distribution and possible co-localisations of inflammatory mediators for microglia (IBA1) and astrocytes (GFAP) as well as the water channel aquaporin 4 (AQP4) in AD and non-AD human brain sections and in transgenic mouse models.

Methods

Human brain samples (Braak stages 2-6) and mouse brain sections from different genotypes (PLB2_{AP}, PLB2_{Tau} and PLB_{WT} controls) underwent dewaxing, antigen retrieval, blocking and antibody application. Immuno-labelling was performed using GFAP, IBA1, AQP4, MOAB2 (for $A\beta$) and CP13 (for phosphorylated tau). Images were obtained using a fluorescent microscope and captured via a digital camera (AxioVision system). Human staining was analysed through ImageJ software and expressed as area stained.

Results

Human samples have significantly elevated levels of the astrocytic marker GFAP in Braak stages 5/6 (severe) compared to Braak stages <2 (low) and 3-4 (moderate). Conversely, non-significant differences over all Braak stages were recorded for IBA1 and AQP4 and all three markers in AD cases appeared non-significant when compared to non-AD cases.

Transgenic mouse samples indicated elevated GFAP levels in PLB2_{AP} and in particular PLB2_{Tau} phenotypes compared to PLB_{WT} (not quantified here). Phosphorylated tau and $A\beta$ appeared to be present in higher levels (qualitatively) within the CA1 hippocampal region.

Conclusion

Our findings in human tissue indicate that neuro-inflammation may only be a late stage occurrence in AD. Qualitative elevations of GFAP in transgenic mouse tissue, particularly in PLB2_{Tau} may imply that phospho-tau could be a trigger of neuro-inflammation, particularly in the CA1 region. Further investigations involving co-staining inflammatory markers with pathological AD hallmarks ($A\beta$ and phospho-tau) may confirm co-localisations and hence specific roles related to neuro-inflammation.

Supervisors: Jie Yeap, Heather Buchanan, Dr. David Koss, Professor Bettina Platt

Role of cAMP and Epac in central nervous system neuronal growth; a comparative analysis between isolated neonatal cortex, spine and dorsal root ganglia cultures

Nasir Rafiq

Background

Cyclic adenosine monophosphate (cyclic AMP or cAMP) as a second messenger is part of intracellular signalling processes which mediate several cellular responses such as cardiac contraction and neurotransmitter release. Recent focus has been on the effects of cAMP on Epac (exchange protein activated by cAMP), in particular Epac 1 and 2. Mainly due to the synergistic impact of Epac and cAMP on promoting central nervous system neuronal outgrowth.

Methods

Sterile isolation of cortical, spinal and dorsal root ganglia (DRG) of neonatal mice pups (range: day 1 – 5) was achieved for neuronal cultures. Neurone cultures were incubated for at least 3 days before undergoing cell lysis and protein extraction with RIPA buffer. Extracted proteins from neuronal cultures underwent validation using a protein assay with Merk's Novogen BCA protein assay kit. Following concentration curve, protein western blot technique will be carried out.

Results

Results pending.

Conclusion

cAMP and Epac play a pivotal role in CNS regeneration and growth, as previous *in vitro* studies in spinal cord injury models have shown exogenous cAMP injections improve axonal regrowth. A detailed mechanism outlining the specific role of cAMP and Epac in neuronal regeneration remains unclear. However, it is clear the loss of cAMP and sequential loss of function from Epac are in-part responsible for inhibition of neuronal growth following spinal cord injury. Therefore, these could play a key role in a combined approach to achieve neuronal axon re-growth following spinal cord injury.

Supervisors: Alba Guljarro-Belmar, Dr. Wenlong Huang



External

Externally Funded Scholarships

Cognitive impairment is associated with mortality in older adults in emergency surgical setting: findings from the Older Persons Surgical Outcomes Collaboration (OPSOC)

Andrew D Ablett

Background

Cognitive impairment is prevalent in older surgical patients, yet the condition is greatly under-recognised and the outcome associated with it is poorly understood. We aim to evaluate the impact of cognition on outcomes in older adults admitted as a surgical emergency.

Methods

Cognition on admission was assessed using the validated Montreal Cognitive Assessment (MoCA) in older emergency surgical patients admitted to five acute surgical units participating in the Older Persons Surgical Outcomes Collaboration (www.OPSOC.eu). The effect of having a low MoCA score (impaired cognition) on relevant outcomes were examined using multivariate logistic regression models, adjusting for age, sex, polypharmacy, haemoglobin, albumin and additionally controlling for patients undergoing surgical intervention.

Results

A total of 539 older patients admitted consecutively to five surgical units during the 2013 & 2014 study periods were included. The median age (IQR) was 76 years (70-82). The prevalence of cognitive impairment using the traditional MoCA cut off score of ≤ 26 was 84.4%, whilst using the recently suggested cut off score of ≤ 23 the prevalence was 61.0%. The emergency operation rate was 13.1% (n=72). Multivariable analyses showed patients with a low MoCA score had increased 30-day mortality (adjusted OR=3.10 (95% CI:1.19-8.11; p=0.021) and an increased length of hospital stay (10 or more days; 1.80 (1.10-2.94; p=0.020) and 14 or more days; 2.06 (1.17-3.61; p=0.012)).

Conclusion

Cognitive impairment assessed on admission is prevalent and may have clinical utility as it is associated with identifying older patients at risk of poor outcomes in the emergency general surgical setting.

Supervisors: Professor Phyo K Myint, Dr. Jonathan Hewitt, Dr. Ben Carter

Funded by Medical Research Scotland

Effect of *in utero* exposure to cigarette smoking to human fetal kidney development

Serena Banh

Background

In utero exposure to maternal smoking is linked to a wide range of fetal developmental abnormalities including low birth weight and smaller kidneys. We have demonstrated changes to human fetal ovaries, testes, and liver, but less is known about the developing fetal kidney. We aimed to characterise and identify phenotypic and molecular changes to the human fetal kidney in relation to maternal smoking status.

Methods

Human fetal kidneys were collected from elective terminations of normally-progressing pregnancies (7-20 weeks of gestation, Scottish Advanced Fetal Research Study, REC 15/NS/0123). Whole kidney extracts were prepared from 67 fetuses. 23 transcripts of key renal developmental genes, renin-angiotensin system (RAS), and kidney injury markers were quantified by qPCR. Statistical analysis was done by ANOVA, linear regression and non-parametric tests as appropriate.

Results

Smoke-exposed kidneys tend to be lighter by 14-16 weeks in both sexes ($p=0.026$). Expression of 11/23 transcripts (5 renal developmental genes, 4 components of RAS, 1 kidney injury marker and 1 hypoxic marker) significantly increased with fetal age, while erythropoietin (*EPO*) transcript was undetectable. *VEGF-A* and *HIF1A*, normally induced by hypoxia, were significantly increased in male fetuses. *BMP7*, *NPHS1* and *NPHS2*, involved in podocyte development were dysregulated in kidneys of smoke-exposed female fetuses. These findings are suggestive of slowed developmental expression patterns in smoke-exposed fetuses.

Conclusion

Maternal smoking leads to smaller kidneys and our data suggests that this manifests as early as 14-16 weeks of gestation. Retarded renal development is a known major contributor to hypertension in adulthood. Moreover, sex-specific patterns of transcript expression may lead to sex-differential susceptibility to renal injuries. We are currently analysing podocyte morphology in the human fetal kidney. Overall, insight on the mechanisms underlying effects of maternal cigarette smoking on fetal kidney development may provide key data to prevent/reduce kidney diseases in adulthood.

Supervisors: Professor Paul A Fowler

Funded by Endocrine Society

The role of HMGB1 in the pathogenesis of colorectal cancer

Sandra Hapca

Background

Colon cancer is a common cancer worldwide with significant mortality. The nuclear protein high mobility group box 1 (HMGB1) has been implicated in the pathogenesis of many cancers by its effects on immune and cancer cell behaviour. Our previous data revealed that cytoplasmic HMGB1 expression is associated with early colon carcinogenesis. We aim to investigate the biological significance of this expression profile.

Methods

CD4⁺ helper T cells, CD8⁺ cytotoxic T cells, FOXP3⁺ regulatory T cells, CD20⁺ B cells and CD68⁺ macrophages were assessed by immunohistochemistry on paraffinised endoscopically retrieved polyp cancer lesions sourced from Grampian Tissue Biorepository (n=25). The invasive cancer margin was identified by a specialist pathologist as the highest intensity HMGB1 staining. The immune cell infiltrate was expressed as number of positive cells per high power field (x20) in the adjacent stroma alongside intensity of nuclear and cytoplasmic HMGB1 staining expression.

Gastrointestinal epithelial cell permeability gene expression (*CLDN2*, *CLDN4*, *OCLN*, *CDH1*, *TJP1*) was assessed by TaqMan Assay RT-PCR to 0, 50 and 100 ng/mL recombinant HMGB1 in Caco2 colonic epithelial cells (ATCC® HTB-37TM). Data was analysed by Livak method.

Results

A robust inflammatory infiltrate was identified adjacent to the invasive cancer margin with a preponderance of CD4⁺ T cells and CD68⁺ macrophages. The subcellular localisation of HMGB1 (nuclear versus cytoplasmic) did not result in phenotypically distinct populations. HMGB1 stimulation significantly decreased the expression of *CLDN4* ($p < 0.008$).

Conclusion

Cytoplasmic HMGB1 expression did not affect the phenotype of the immune cell infiltrate but its effect on cell function remains unknown. HMGB1 inhibits the expression of the basal tight junction gene, *CLDN4*. Claudin-4 is barrier forming by closure of pores. HMGB1 induced loss of claudin-4 may increase gastrointestinal permeability allowing bacterial translocation. Understanding HMGB1 driven biology in cancer polyps could identify an important mechanism for early carcinogenesis.

Supervisors: Dr. Mairi McLean, Professor Graeme Murray

Funded by Medical Research Scotland

Does size and direction of osteotomy in orthognathic surgery affect risk of subsequent plate removal?

Samuel Kent

Background

Metal plate removal is a common complication of mandibular osteotomy with between 3.5% and 27.5% of patients requiring removal of some or all of their hardware. However, little is known about the risk factors for removal. We hypothesised that large advances and setbacks may result in stretching of overlying soft tissues which could increase risk of dehiscence and infection, and hence plate removal.

Methods

Retrospective case review of all orthognathic surgery carried out at Aberdeen Royal Infirmary between May 2011 and May 2017.

Results

One hundred and ninety nine mandibular osteotomies were carried out, and full surgical records were available for 166 of these. 85 advances and 81 setbacks were identified, with mean advance +6.77mm (+1 to +15mm SD 3.00mm) and mean setback of -4.66mm (-1 to -10mm, SD 2.00mm). 25 patients underwent subsequent plate removal, 11 who had undergone BSSO advance and 7 setback. There was no significant correlation between size of advance and plate removal.

Conclusion

Previous risk factors identified for subsequent plate removal include smoking, age, female sex, stainless steel plating systems, mandibular plates, increased number of plates and plates placed close to the upper border of the mandible. We showed that there is no correlation between increased magnitude of mandibular advancement or setback and subsequent plate removal.

Supervisors: Mr. Roderick Morrison

Funded by Medical Research Scotland

SMOM and Wnt- β -catenin asymmetry pathway in *Caenorhabditis elegans*

long Man Tung

Background

The Wnt signalling pathway is an important pathway in embryonic development. Beta-catenin is an important component in the canonical Wnt signalling pathway and is conserved across most species. Beta-catenin is also an important component in cell adhesion in complexes called adherens junction. However, in *C. elegans* there are 4 homologues of beta-catenin that have undergone functional specialisation. The lack of certain Wnt signalling pathway components also indicates the rewiring of the Wnt-signalling pathway in *C. elegans*. Previous studies showed *C. elegans* beta-catenins interact with a set of 3 novel, related molecules, termed synthetic more mesoderm (SMOM).

Methods

Loss of function tests were performed on these molecules (SMOM-1, SMOM-2 and SMOM-3) to demonstrate the role of these molecules in the derived Wnt asymmetry pathway within *C. elegans*. In order to determine the subcellular distribution of one of these molecules, SMOM-1, a CRISPR-engineered GFP fluorescent tag was added to allow us to visualise the protein through confocal imaging.

Results

Loss of function tests for SMOM-1 displays the same phenotype as when the Wnt pathway is inhibited in *C. elegans*, where the endoderm, mesoderm and stomodeum blastomere was unable to differentiate into mesoderm and endoderm cells, instead only mesoderm cells are produced. The SMOM-1 GFP-tagged protein was shown to localise to the membrane of embryonic cells.

Conclusion

These results suggest that the SMOM proteins form part of the machinery that responds to the extracellular Wnt signal.

Supervisors: Dr. Jonathan Pettitt

Funded by The Genetics Society

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Further your academic interest

Below are a selection of useful organisations and websites to help further your interest in academic medicine as a student.

Aberdeen Student Society for Academic Medicine (ASSAM)

“The Aberdeen Student Society for Academic Medicine (ASSAM) was established in 2012 with the hope to encourage undergraduate interest in medical research. Even though their primary aim is to inspire medical students to pursue a career in academia, we also try to highlight the importance of basic research skills and critical appraisal in normal clinical practice”

www.assam.nsamr.org

E: assam@nsamr.ac.uk

Fb: **AberdeenASSAM**

Aberdeen Clinical Academic Training (ACAT)

Training programmes and support for postgraduate clinicians in Aberdeen.


www.abdn.ac.uk/smmsn/acat

National Student Association of Medical Research (NSAMR)

“National Student Association of Medical Research (NSAMR) is a non-profit, non-governmental and non-partisan student-led organisation representing an association of medical research societies nationally”

www.nsamr.org





**The following academic units and
clinical departments provided supervision**

Aberdeen Biomedical Imaging Centre

Aberdeen Maternity Hospital

Ageing Clinical & Experimental Research Team

Arthritis and Regenerative Medicine Group

Chronic Diseases Research Group

Department of Gastroenterology, NHS Grampian

Department of General Surgery, NHS Grampian

Department of Rheumatology, NHS Grampian

Department of Trauma and Orthopaedic Surgery, NHS Grampian

Gastrointestinal Research Group

Health Services Research Unit

Institute of Applied Health Sciences

Institute of Dentistry

Institute of Medical Sciences

MRC Centre for Medical Mycology

Oral and Maxillofacial Surgery, NHS Grampian

The Rowett Institute of Nutrition and Health