Abstracts

Selected Abstracts of the 14ᵗʰ International Workshop on Neonatology

THE REVOLUTION OF MICROBIOMICS
NUTRITION, BACTERIA AND PROBIOTICS IN PERINATAL AND PEDIATRIC HEALTH

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The Workshop has been organized with the patronage of the Italian Society of Neonatology (SIN), the Italian DOHaD (Developmental Origins of Health and Disease) Society (SI-DOHaD), the Italian Society of Clinical Biochemistry and Clinical Molecular Biology (SIBioC), the Union of European Neonatal and Perinatal Societies (UENPS), the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), the Union of Middle-Eastern and Mediterranean Pediatric Societies (UMEMPS), the European Association of Perinatal Medicine (EAPM), the Italian-Romanian Pediatric Society (IRPS) and the Italian-Arabian Pediatric Society (IAPS).

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Giovanni Ottonello (Cagliari, Italy), Denis Pisano (Cagliari, Italy), Melania Puddu (Cagliari, Italy)

Table 1 (ABS 46). Comparison between live patients (group A) and deceased patients (group B).

	Group A (n = 55)	Group B (n = 4)	p-value
Caesarean section	20 (36.4%)	4 (100%)	**< 0.05**
CTG anomalies	9 (16%)	2 (50%)	0.09
Placental anomalies	6 (10%)	1 (25%)	0.40
Endotracheal intubation < 10 minutes	28 (51%)	4 (100%)	≥ 0.05
Apgar ≤ 5 at 10 minutes	25 (45%)	3 (75%)	0.896
pH at blood gas analysis	7.066 ± 0.202	7.065 ± 0.113	0.330
BE at blood gas analysis (mmol/L)	-13.95 ± 5.368	-17.8 ± 5.027	0.402
ECG anomalies during cooling	21 (38%)	1 (25%)	0.598
HR during cooling (bpm)	97.8 ± 16.259	116.25 ± 7.77	0.229
MAP during cooling (mmHg)	49.64 ± 2.00	40.75 ± 9.73	0.184
UO during cooling (ml/kg/h)	1.6 ± 0.439	0.7 ± 1.05	0.062
EF < 55% during cooling	18 (33%)	1 (25%)	0.749
PPHN	12 (22%)	3 (75%)	**0.018**
Inotropes	31 (56%)	4 (100%)	≥ 0.05
Troponine T ≥ 0.1 µg/L	10 (33%)	1 (25%)	0.735

CTG: cardiotocography; BE: base excess; HR: heart rate; MAP: mean arterial pressure; UO: urinary output; EF: ejection fraction; PPHN: persistent pulmonary hypertension of the newborn.

(19.5%) [3]. In the comparison between patients with pathological (n = 31) and normal MRI (= 23), we could not find any statistically significant difference. Regarding deceased patients (n = 4), they were all born by cesarean section, and in 3/4 of the cases, a PPHN was documented (p < 0.05), demonstrating how PPHN is an important cause of mortality in PA (**Tab. 1**). As regards inotropes, dopamine determined an increase in UO in 66% of cases within 48 hours from the start of treatment, while 23 patients required dobutamine therapy at an average dose of 5-10 mcg/kg/min, with an improvement in EF values already after 24 hours of therapy in 82% of cases and of PPHN within 24 hours in 66% of cases.

CONCLUSIONS

PA is still a significant problem at birth, with a worsened prognosis if associated with PPHN. Therefore, it could be useful to promote effective antenatal care and accurate evaluation of the modalities of birth, in order to reduce the extent of PA. In addition, preventive use of dopamine and dopamine at doses ≤ 10 mcg/kg/min could be effective in improving EF, PPHN, and UO, thus ameliorating the outcome of these patients.

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ABS 47

CAPICE – CHILDHOOD AND ADOLESCENCE PSYCHOPATHOLOGY: UNRAVELLING THE COMPLEX ETIOLOGY BY A LARGE INTER-DISCIPLINARY COLLABORATION IN EUROPE

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ESR 1: KRATIKA AGARWAL (THE UNIVERSITY OF TWENTE, THE NETHERLANDS)

Harmonised phenotypes for emotional problems and ADHD

This study aims to harmonize questionnaire item data with an objective of having one phenotype that is comparable across various cohorts. Our focus here is on internalizing problems and ADHD symptoms. In order to harmonize questionnaire item data, we used the Western Australian Pregnancy Cohort study (RAINE) dataset as it consists of both Child Behaviour Checklist (CBCL) and the Strength and Difficulties Questionnaire (SDQ) data on 10-year-old children. We were able to identify common dimensions in SDQ and CBCL questionnaire data from Australian data on 10-year-olds. The psychometrics analysis showed

that particular subsets of CBCL and SDQ items can be used together but also separately to measure emotional problems and ADHD.

ESR 2: ANDREA GIUSEPPE ALLEGRINI (KING'S COLLEGE LONDON, UK)

Genomic prediction of cognitive traits in childhood and adolescence

Methodological advances in the flourishing field of polygenic epidemiology, coupled with constantly increasing sample sizes in genome-wide association studies (GWAS), call for a practical application of current state-of-the-art methodologies to complex trait prediction.

Here we set out to test the extent to which we can maximize prediction accuracy of cognitive and educationally relevant traits in a sample of 7,026 individuals representative of the UK population.

These results set the lower bound for the polygenic score prediction of cognitive-related traits and serve as a benchmark against which we compare different prediction models. We are building our models by leveraging several large publicly available GWAS summary statistics and testing different multivariate GWAS methods, and polygenic score approaches with the aim of maximizing variance predicted and educational achievement. We will report on the most predictive combination of modeling approaches to trait prediction.

ESR 3: ESHIM SHAHID (VU UNIVERSITY, THE NETHERLANDS)

Internalising problems are highly prevalent in childhood and correlate strongly with anxiety, depression and related disorders in adulthood (Hannigan et al., 2017). It is known that internalizing problems are heritable (Polderman et al., 2015) but research thus far has been unsuccessful in identifying common genetic variants that underlie these behaviors. In this large-scale genome-wide association meta-analysis (GWAMA), our primary aim is the identify common genetic variants that influence the development and course of internalizing symptoms across childhood and adolescence. Cohorts within and beyond the CAPICE consortium with genotypic data and phenotypic data on childhood internalizing problems are invited to participate in this study. The inclusion of a large number of cohorts with thousands of individuals will help to yield sufficient power in order to detect small genetic effects. With this study, we hope to improve our understanding of the development and progression of mood and related disorders in youth.

ESR 4: VILLE KARHUNEN (IMPERIAL COLLEGE LONDON, UK)

My project aims to improve understanding of the relationship between multi-omic variation and behavioral traits, especially those related to adolescent attention-deficit hyperactivity disorder (ADHD), and to apply advanced statistical methods in order to exploit multi-omics datasets as efficiently as possible. The first specific objective was to examine the association between exposure to maternal smoking (which is known to be associated with offspring ADHD) and offspring DNA methylation. Smoking during pregnancy is known to alter DNA methylation in newborns. We have been studying whether the changes in DNA methylation in the exposed offspring persist into adolescence and adulthood and whether these changes mediate the effect of intrauterine smoke exposure on later life health outcomes. Our findings indicate a long-lasting effect of exposure to maternal smoking on offspring DNA methylation and that some of these changes may act as a potential mechanism between maternal smoking and later-life diseases in the exposed offspring.

ESR 5: OMOWONUOLA AKINGBUWA (VU UNIVERSITY, THE NETHERLANDS)

Longitudinal cohort-based studies have shown that the onset of various psychiatric disorders in adulthood is often preceded by psychiatric symptoms and disorders in childhood and adolescence (Kessler et al., 2007, Rao and Chen, 2009). Similarly, childhood psychopathology has been found to be associated with physical traits including BMI, as well as adversely affecting cognitive traits like IQ and educational attainment (Pine et al., 2001, Singh et al., 2013, Costello and Maughan, 2015). These individuals typically continue to have less favorable outcomes in areas of adult functioning related to health, SES and social relationships/isolation (Copeland et al., 2015, Costello and Maughan, 2015). This project aims to perform large-scale analyses of the genetic overlap between adult psychiatric disorders and related traits, and childhood and adolescent psychiatric phenotypes. To achieve this, this study will use available GWAS summary statistics data on adult psychiatric disorders and related traits to construct polygenic risk scores (PRS), as well as phenotype data on childhood internalizing behavior, ADHD/Attention Problems and Social Problems from multiple suitable cohorts.

ESR 6: ELIS HAAN (UNIVERSITY OF BRISTOL, UK)

My Ph.D. is focusing on alcohol use, smoking and caffeine use in mothers during pregnancy and my main outcome of interest is ADHD in offspring. More specifically I am looking at associations between genetic variants of consumption behavior and mental health outcomes in children. I am currently working

with three projects: "Associations between alcohol, tobacco and caffeine consumption in pregnancy and externalizing disorders in offspring: a systematic review and meta-analysis". Negative control study for comparing maternal and paternal consumption behavior with offspring mental health outcomes. Phenome-Wide association study (PheWAS) for looking at if genetic variants associated with consumption behavior are associated with mental health phenotypes across the lifespan in different time points using ALSPAC data.

ESR 7: ELIZABETH DIEMER (ERASMUS UNIVERSITY MEDICAL CENTRE ROTTERDAM, THE NETHERLANDS)

Mendelian randomization (MR), a type of instrumental variable model in which single nucleotide polymorphisms are proposed as instruments, is increasingly popular. Like all instrumental variable models, MR relies upon a set of unverifiable assumptions, which researchers often support using subject matter knowledge alone. However, the instrumental variable model implies certain inequalities, offering an empirical method of falsifying (but not verifying) the underlying assumptions. While these instrumental inequalities are said to detect only extreme violations of instrumental variable assumptions in practice, they have not been used in settings with multiple proposed instruments. In our study, we plan to demonstrate the utility of the instrumental inequalities in identifying violations of the assumptions required for MR analyses of prenatal exposures and offspring outcomes in the Generation R cohort, a population-based cohort based in the Netherlands, across SNPs jointly proposed as instruments.

ESR 8: LAURA SCHELLHAS (UNIVERSITY OF BRISTOL, UK)

A phenome-wide association study to Investigate the association of polygenic risk scores for alcohol, tobacco and caffeine consumption and a range of mental health phenotypes in three generations in ALSPAC (adults, adolescents, and pregnant women). A meta-analysis of epigenome-wide association studies investigating the association of caffeine consumption during pregnancy and offspring DNA methylation. A systematic review is summarizing the association of maternal alcohol, tobacco and caffeine consumption during pregnancy and offspring methylation.

ESR 9: HEMA SEKHAR REDDY RAJULA (UNICA, ITALY)

We worked on CAPICE data catalog. There are 16 cohorts available for CAPICE data catalog. ALSPAC is one of the cohorts from the University of Bristol.

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a transgenerational prospective observational study investigating influences on health and development across the life course. We worked on ALSPAC data and trying to pull the list of variable names from the ALSPAC variable catalog. We added the description as well to the listing. It might be interesting from a metadata perspective as this might give a longitudinal perspective on certain variables. In the future to perform the multi-site analyses most efficiently, the aim is to build a facility that allows analyzing all data available over sites without necessarily having access to the raw data. The role of big data in neuropsychiatric disorders: a focus on metabolomics. Neuropsychiatric disorders are a heterogeneous group of conditions with multiple diatheses. Indeed, the trajectory leading to a diagnosis of a neuropsychiatric disorder is likely modulated by the interplay of genetic and environmental factors. Specific criteria guide the identification of a specific neuropsychiatric phenotype (diagnosis), the use of psychometric tools (scale and/or questionnaires), and, to a certain extent, by biomarkers, including those derived by "omics" approaches. The large datasets obtained by the integration of clinical and omics data need specific analytical pipelines. Indeed, the term big data refers to highly complex, heterogeneous and high-dimensional large-scale datasets. Big data approaches are hypothesis-generating and discovery-oriented, with the goal of revealing the hidden patterns or information behind complex data using computer science and, statistical approaches.

ESR 10: ASHLEY THOMPSON (KAROLINSKA INSTITUTET, SWEDEN)

Long-term negative outcomes in ADHD

ADHD has impairing consequences for the individual, the family, and the society. This mental illness has been associated with increased risk of premature mortality, and other negative outcomes such as criminality, suicide attempts, substance use problems, and transport accidents. While effective pharmacological treatments exist to mitigate these outcomes, there is a current treatment gap for this vulnerable group. This gap is exemplified by the current lack of knowledge of how to best identify the subset of individuals with ADHD with the highest risk for severe outcomes. Thus, the overarching goal of the Ph.D. project is to identify individuals with ADHD in need of special attention, as well as to understand the features that characterize this group. This aim will be realized with large, longitudinally collected data from two substantial cohorts to predict adverse outcomes in ADHD patients. Supervised machine learning techniques will be used

in order to create a prediction model that can hopefully be turned into a checklist for clinical use. Therefore, it is expected that this project will lead to improved prediction and identification of individuals at high risk for negative events. This innovation will help inform targeted prevention and treatment for those who would benefit the most, thus lowering costs for the individuals as well as for the society at large.

ESR 11: SABRINA DOERING (UNIVERSITY OF GOTHENBURG, SWEDEN)

Anxiety disorders are the most prevalent mental disorders in childhood and adolescence. When left untreated, they often lead to psychiatric outcomes in adulthood, such as anxiety disorders, depression, and substance abuse. The overarching goal of my Ph.D. project at the University of Gothenburg and within CAPICE is to create prediction models for both psychiatric and functional outcomes, e.g., unemployment, criminal convictions, sick leave, in young adulthood for adolescents who present with various degrees of anxiety.

ESR 12: MARICA LEONE (JANSSEN-CILAG AB, SWEDEN)

Aim

To investigate the relationship between early-onset depression and the subsequent development of any somatic medical outcomes. The purpose of this study is to provide valuable insights into the long and short-term effects of depression assessed at a young age.

Statistical analysis

This study will test all the individuals born in Sweden between 1982 and 1996 with a follow up until December 31st, 2013. For this cohort, exposure will be a diagnosis or a filled prescription of one or recurrent depressive episodes between age 3 and 19, and the data will be gathered from the National Patient Register (NPR), Prescribed Drug Register (PDR) and the Pastill register, a comprehensive clinical database for child and adolescent psychiatry in Stockholm established in 2001. Socioeconomic status and birth year will be considered as potential confounders.

FIGURES

In **Fig. 1** the website of CAPICE Project (https://www.capice-project.eu) is presented; **Fig. 2** is the picture of the group of the Early Stage Researchers (ESRs).

Figure 1 (ABS 47). The website of CAPICE Project (CAPICE: Childhood and Adolescence Psychopathology: unravelling the complex etiology by a large Interdisciplinary Collaboration in Europe).

Figure 2 (ABS 47). The group of the Early Stage Researchers (ESRs).

ABS 48

NEONATAL PARECHOVIRUS SEPSIS: A CASE REPORT

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INTRODUCTION

During the first month of life, more than 10% of the neonates is affected with an infectious episode, 2% of these infections start *in utero*. The most common infections are urinary tract infection, sepsis, septicemia, and meningoencephalitis. The most common infectious agents are *E. coli*, *Streptococcus agalactiae Group B*, *Listeria Monocytogenes*, *Enterococcus*, *Staphylococcus Aureus*, *Moraxella*, HSV, Enterovirus and Parechovirus. We describe a case report of Parechovirus neonatal sepsis.

CASE REPORT

Male of 24 days of life, born at 40 weeks gestation, spontaneous vaginal delivery, birth weight 3,180 g. Maternal vaginal swab negative. He comes to ER for fever (temp. max 38.8°C) which has been present for some hrs. Physical examination: discrete general status, pale/pink skin, CRT 2 sec, HR 190 bpm, SaO_2 98% in RA, RR 40/min, alert, good cry and suction, anterior fontanelle soft and flat. No meningeal signs. The rest of the physical examination is normal. In the beginning, parenteral hydration is started with NS. Laboratory tests: WBC 5,020/mL (N 70%), PCR 5.7 mg/dL; PCT 0.63 ng/mL, ABG wnl, LFT and KFT wnl, urine test normal. Blood, liquor and urine cultures are started, and antibiotics (ampicillin and gentamicin) are given. After 24 hours a worsening general appearance is observed with temp. max 40°C, irritability, moaning cry, marble skin, cold and pale extremities, CRT 3 sec, HR 190-220 bpm, SaO_2 98% in RA, RR 40/min, BP 94/48 mmHg. Laboratory tests: WBC 4,020/mmc (N 52.5%), PCR 8.3 mg/dL, PCT 1.04 ng/mL. Therefore he is transferred to the PICU for severe neonatal sepsis. Acyclovir is added to the antibiotic therapy, and viral PCR is performed on blood and nasopharyngeal secretions. On both samples, Parechovirus are confirmed. During the following days, a progressive improvement is shown: after 3 days fever stops, WBC increase to 7,430/mL, with a PCR of 0.6 mg/dL. Acyclovir has been stopped after 3 days due to negative PCR on the blood of HSV, and after 7 days of antibiotic therapy has been stopped too.

CONCLUSIONS

Parechovirus infections are common during neonatal age with a prevalence of 5%. They are a common cause of neonatal fever with sepsis-like illness and neurologic symptoms; these require hospitalization mainly during summer time. RT-qPCR is the gold standard for the diagnosis. Therapy comprehends mainly supportive treatments: the antiviral agent has been proved to be effective for parechovirus. In severe cases, Pleconaril has been considered for compassionate use. Acyclovir is not effective in this infection.

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ABS 49

JOURNEY OF FIRST YEAR OF MY PH.D. AT UNIVERSITY OF CAGLIARI

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