Croatian Institute for Brain Research (CIBR)
School of Medicine, University of Zagreb

9-11th April 2018, ZAGREB

EU Network on Brain Malformations
1st Neuro-MIG Training School

GENOMICS AND IMAGING OF MALFORMATIONS OF BRAIN DEVELOPMENT

Neuro-MIG

Sponsored by
EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

Organized by
EUROPEAN NETWORK ON BRAIN MALFORMATIONS

EU COST Action 11618

Training school committee

Hülya Kayserili, Koç University, School of Medicine, Istanbul, Turkey, Chair, hkayserili@kuh.ku.edu.tr

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Zdravko Petanjek, School of Medicine, University of Zagreb, Croatia

Ivica Kostović, School of Medicine, University of Zagreb, Croatia

Administrative support

Željka Pavlović, School of Medicine, University of Zagreb, Croatia

Iva Šimunić, B-Travel d.o.o., Zagreb, Croatia

Venue

Croatian Institute for Brain Research, School of Medicine University of Zagreb
Šalata 12, Zagreb, CROATIA

Neuro-MIG

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EUROPEAN NETWORK ON BRAIN MALFORMATIONS

(EU COST ACTION: 16118)

GRAZIA M.S. MANSINI

primary proposer

Erasmus MC, Rotterdam, The Netherlands

Among congenital brain disorders, malformations of cortical development (MCD) are a group of rare diseases, but constitute a major cause of chronic epilepsy and psychomotor disability worldwide. Little is known about the natural history, and no curative therapy exists. The etiology is mainly genetic, and rarely environmental or multi-factorial, but diagnosis requires special expertise among neurodevelopmental disorders. The emergence of novel neuroimaging and genomic technologies potentially allows rapid and accurate characterization and gene discovery, but challenges scientists and clinicians in efficiently interpreting and translating these data for the benefit of patients. In Europe, expertise on MCD is very fragmented and confined to the personal interest of a few experts and basic scientists studying cortical development are not always connected with clinicians. This COST Action will, for the first time, bring together clinicians and researchers in the field of brain malformations, to create the interdisciplinary, pan-European Network Neuro-MIG, advancing the understanding of MCD pathophysiology and translating this knowledge to improve the diagnostic and clinical management of the patients. This Action will harmonize MCD classification, based on the advances in genetics and neuroimaging. It aims to develop guidelines for clinical management, create best practice diagnostic pathways, coordinate databases from different countries to utilize them for collective research initiatives focused at developing appropriate therapies, identify common pathophysiological mechanisms through collaborations, educate young clinicians and scientists, and stimulate translational and transnational exchange. This Action will join forces of MCD experts to reduce health care costs and increase the quality of life of the affected individuals and their families.

(Descriptions are provided by the Actions directly via e-COST.)

WELCOME TO ZAGREB FOR THE FIRST Neuro-MIG TRAINING SCHOOL!

It is a great honor and pleasure to welcome you wholeheartedly here to Zagreb, on the occasion of the 1st Neuro-MIG Training School „Genomics and Imaging of Malformations of Brain Development," on behalf of the Organizing Committees and the European Network on Brain Malformations. Three exciting days of a Training School ahead of us, are meant to be a meeting of lively and fruitful discussions among speakers - trainers, and trainees, clinicians and scientists of various disciplines related to early brain development and its malformations. We will discuss the implementation of cutting-edge neuroscience research, new genomics, and neuroimaging technology in health care, diagnosis, follow-up, and treatment of the MCD.

We have invited eminent speakers from around the world who will explore important aspects of normal and disturbed brain development, including cellular and molecular mechanisms regulating cell number and diversity, migration and circuit assembly from the very beginning of the cortical plate formation. The use of new genomics sequencing technology and neuroimaging in early diagnosis and treatment of developmental neurological, cognitive and mental disorders will be extensively discussed as an important topic of the training.

We are grateful to all invited speakers, leading experts in their fields, for their acceptance to participate. Their input will be an invaluable contribution to the overall quality of the event. We are especially grateful to those speakers who accepted the last minute invitation and helped us to complete the demanding training program.

The funding for the 1st Neuro-MIG School was achieved by the enthusiastic work of the members of the Network on Brain Malformations and the European Community through the Cooperation for Science and Technology (COST), Action CA16118. We are very grateful for their generous contributions.

The 1st Neuro-MIG Training School aims to educate young clinicians and scientists, such as clinical geneticists, neonatologists, gynecologists, radiologists, pediatric neurologists and developmental neuroscientists, on the importance of the use of new genomics and neuroimaging technology in early diagnosis and treatment of developmental neurological, cognitive and mental disorders, as well as to encourage and facilitate their joining the research initiatives.

We believe that International cooperation in implementation of the program of this Training School will have a great impetus in our next scientific endeavours and Neuro-MIG Schools to be held. The organizers and a long list of trainers wish you a very enjoyable and productive time on the Šalata hill in Zagreb and look forward to an exciting school!

Nataša Jovanov Milošević

Chair of the Local organizing committee

Neuro-MIG

1st Neuro-MIG Training School

GENOMICS AND IMAGING OF MALFORMATIONS OF BRAIN DEVELOPMENT

9-11th April 2018, ZAGREB

PROGRAMME

1st Day - 9th April 2018, Monday

8:15-9:00 Registration

9:00-9:05 Welcome Address – Director of the CIBR

9:05-9:15 European Networks on Brain Malformations COST CA16118

Session 1: Introduction to brain development

Chairpersons: Nataša Jovanov Milošević and Miloš Judaš

9:15-10:00 Ivica Kostović
The microstructure of the laminar compartments in the cerebral wall: histological-MRI indicators of the typically developing human brain

10:00-10:30 Zdravko Petanjek
Dangerous trip for legal immigrants - cortical GABAergic neurons: dispersed origin and expanded time window of production

10:30-11:15 Orly Reiner
Developmental and cellular aspects of the brain
DISCUSSION

11:30-12:00 **Coffee Break**

Session 2: The role of clinical geneticist and the impact of NGS on MCD

Chairpersons: Hülya Kayserili and Andrew Fry

12:00-12:30 Grazia Mancini
What is the role of the clinical geneticist in the diagnosis of prenatal MCD

12:30-13:00 Peter Bauer
The input of NGS Technology on the diagnosis of Brain Malformation and Identification of Novel Genes
DISCUSSION

13:00-14:30 **Lunch**

Session 3: Case Discussions I. Postnatal Cases

Chairpersons: Gazia Mancini / Andrew Fry / Maha Zaki / Peter Bauer

14:30-15:15 Postnatal cases (solved) - Trainers / Trainees

15:15-16:00 Postnatal cases (unsolved) - Trainers / Trainees

16:00-16:30 **Coffee Break**

Session 4: Team work start-up

Chairpersons: Hülya Kayserili / Maarten Lequin / Maha Zaki / Nataliya Di Donato

16:30-18:00 Team work (in four groups)
Nationwide / Institutional solutions for the definite diagnosis, follow-up strategies and treatment applications, research orientation of MCD group of disorders

20:00 **Get Together Dinner (Trainers and Trainees)**

2nd Day - 10th April 2018, Tuesday

Session 5: Child with neurodevelopmental disorders: Challenges to be met

Chairpersons: Orly Reiner and Nataša Jovanov Milošević

9:30-10:00 Andrew Fry
Polymicrogyria – clinical and molecular considerations

10:00-10:30 Maha Zaki
Midbrain and hindbrain anomalies

10:30-11:00 Nataliya Di Donato
Lissencephaly: molecular diagnostics, management and counseling
DISCUSSION

11:00-11:30 **Coffee Break**

Session 6: How to reach definite diagnosis on MCD related disorders

Chairpersons: Andrew Fry/ Hülya Kayserili / Nataliya Di Donato / Maha Zaki

11:30-13:00 How to solve the cases?
- Clinical neurologist approach (M. Zaki)
- Clinical dysmorphologist approach (H. Kayserili)
- Medical Geneticist approach (A. Fry)
- Combined approaches to solve the case (N. Di Donato)

13:00-14:00 **Lunch**

Session 7: Clinical Radiology

Chairpersons: Maha Zaki and Nataliya Di Donato

14:00-14:45 Maarten Lequin
Neuroradiological approach for MCD

14:45-15:30 Gustavo Malinger
Early prenatal ultrasonographic findings suggestive of malformations of cortical development
DISCUSSION

15:30-16:00 **Coffee Break**

Session 8: Case Discussions II. Antenatal Cases
Radiological Assessment of MCD

Chairpersons: Maarten Lequin and Gustavo Malinger

16:00-16:45 Antenatal Cases (solved / unsolved) Trainers / Trainees discussion

16:45-17:30 How to read MRIs
Lissencephaly/ tubulinopathies and others; Trainers / Trainees discussion

20:00 **Dinner Free night**

3rd Day - 11th April 2018, Wednesday

Session 9: Future of Research and its impact on Neurodevelopmental Disorders

Chairpersons: Zdravko Petanjek and Andrew Fry

9:30-10:00	Renzo Guerrini
	Malformations of cortical development and human phenotypes: directions for research
10:00-10:30	Nadia Bahi-Buisson
	The phenotypic spectrum of Dyneinopathies: from lissencephaly to Spinal Muscular Atrophy with lower limb predominance
10:30-11:00	Miloš Judaš
	Cortical changes in holoprosencephaly and Walker – Warburg lissencephaly
	DISCUSSION
11:00 -11:30	**Coffee Break**

Session 10 Novel tool, organoids

Chairperson: Nadia Bahi-Buisson

11:30-12:30	Orly Reiner
	Brain organoids for studying normal and diseased brain development
	DISCUSSION
12:30-13:30	**Lunch**

Session 11 Clinical & molecular genetics and radiology of MCD

Group presentations

Chairpersons: Grazia Mancini / Renzo Guerrini / Maha Zaki

13:30-14:15	Quick Quiz (what I have learned on molecular genetics and radiology of neurodevelopmental disorders) - Trainers / Trainees
14:15-15.30	Group Presentations (team work)
15:30-16:00	**Coffee Break**

Session 12 Wrap-up and Feedback

Chairpersons: Hülya Kayserili and Nataša Jovanov Milošević

16:00-17:00	Wrap-up discussion - Trainers / Trainees
	Farewell

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INVITED SPEAKERS

IVICA KOSTOVIĆ

Professor Emeritus, MD, Ph.D.
Croatian Institute for Brain Research, Honorary Director
Croatian Society for Neuroscience, President
School of Medicine, University of Zagreb
Šalata 12, 10000 Zagreb, Croatia
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Education: He obtained his degrees at the University of Zagreb: M.D. degree in School of Medicine, M.Sc. degree in Faculty of Natural Sciences and D.Sc. Degree in School of Medicine. He was Fogarty International Fellow & Fullbright postdoctoral fellow at the Johns Hopkins University School of Medicine (Baltimore, MD).

Profesional activities: He has been employed at the School of Medicine in Zagreb since 1965. He was visiting an assistant professor of neuropathology and research fellow at the Department of Neuroscience, Harvard Medical School (Boston, U.S.A.). He was director of the Croatian Institute for Brain Research (2000-2013). Currently serves as a member of National Council for Science, Higher Education and Technological Development and Professor Emeritus at the University of Zagreb. Research: He was the principal investigator on four consecutive Joint board projects with P. Rakic and P.S. Goldman-Rakic (Department of Neurobiology, Yale University School of Medicine) from 1979 to 1991. At the School of Medicine, he served as Vice-dean for Research and Dean. He is a founder and honorary director of Croatian Institute for Brain Research. He also served as Minister of Science, Vice-president of the Croatian Government, member and Deputy Speaker of Croatian Parliament, President of the Board of Croatian Science Foundation and ERC Panel Member.

Awards & Honors: Spinoza Professor (University of Amsterdam); Rudjer Boskovic Award (Croatia); The Flag of the United States of America; Casting Lecture; National Science Award for Biomedicine and Health - Award for Lifetime Achievement (Croatia). Membership: Society for Neuroscience, International Brain Research Organization, Federation of European Neuroscience Societies, Academia Europaea, European Dana Alliance for the Brain (EDAB), Croatian Society for Neuroscience (president). He is a Full Member of Croatian Academy of Sciences and Arts. Main research interest: human developmental neurobiology & neuroanatomy. Major contributions: discovery of the transient fetal subplate zone; first description of early bilaminar synaptogenesis in the human cerebral cortex; pioneering studies of connections between human fetal thalamus and visual, auditory, somatosensory and frontal cortex. These discoveries had an impact on Abortion Law (US Supreme Court).

THE MICROSTRUCTURE OF THE LAMINAR COMPARTMENTS IN THE CEREBRAL WALL: HISTOLOGICAL-MRI INDICATORS OF THE TYPICALLY DEVELOPING HUMAN BRAIN

Ivica Kostović

Normal laminar, areal, modular and connectional organization of the cerebral cortex is the result of series of neurogenetic events (proliferation, migration, neural aggregation, axonal growth synaptogenesis dendritic differentiation, myelination) which occur in spatially defined fetal compartments and in the precise time schedule. Accordingly, the disturbed neurogenetic events will cause abnormal structural organization, disturbed developmental schedule and will eventually lead to a change of wiring of the brain. In order to present structural criteria for normal development of the human cortex, we correlated laminar development using histological in vivo and in vitro MRI approaches. Despite differences in the resolution of histological sections and MR scans we have demonstrated three laminar organization: ventricular zone (VZ), intermediate zone (IZ) and cortical plate (CP) as early as 11 weeks postovulation (POW). It is very interesting that MR analysis demonstrated crucial step in the formation of transient subplate zone around 13POW which is characteristic for primate development. During midgestation, an excellent correlation was seen between histological and MR images. The following compartment ware identified: (1) VZ; (2) subventricular zones (SVZ); (3) IZ with growing axonal strata and migratory neurons; (4) voluminous subplate zone (SP) abundant in ECM as main synaptic and axonal growth zone; and (5) densely aggregated CP. Marginal zone (MZ) is too thin to be clearly visualized on the MR images. The axons of IZ and cells of outer SVZ form multilayered cellular-fibrillar compartment The correlation between histological sections and conventional MR images was also observed in early preterm below 34 PCW during accumulation of thalamocortical fibers and penetration of the cortical plate. In late preterms, after 34 PCW the resolution of cerebral compartments is less prominent due to the development of white matter segments (crossroads, sagittal strata, centrum semiovale and gyral white matter, WM). However, transient SP is still visible at the interface of gyral white matter and cortical plate. In the neonatal brain, there is a significant reduction of ventricular proliferative zones and significant growth of white matter segments and formation of cortical convolutions. Despite these events, SP remnant is still present as a plexiform band at the interface of layer VI and gyral WM. The data presented in this review are essential for the study of the radial vulnerability of different classes of axonal connections. We propose a concept of radial vulnerability as an excellent framework for studies of normal and abnormal human cerebral cortex development *(Supported by Croatian Science Foundation).*

ORLY REINER

Professor, Ph.D.
The Incumbent of the Berstein-Mason professorial chair of Neurochemistry
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Weizmann Institute of Science
234 Herzl St.
Rehovot 7610001, Israel
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Education:

B.Sc. 1975-1978	Hebrew University, Faculty of Agriculture, Agriculture
M.Sc. 1983-1985	Hebrew University, Faculty of Agriculture, Microbiology
Ph.D. 1985-1990	Weizmann Institute of Science, Human Molecular Genetics

Profesional activities:

2010-present	Professor	Weizmann Institute of Science
2002-2010	Associate Professor	Weizmann Institute of Science
1993-2002	Senior scientist	Weizmann Institute of Science
1990-1993	Postdoctoral fellow	Baylor College of Medicine

ERC LS5 committee member 2007-2015.

Other experience

Head of Weizmann IACUC committee, Aug 2011- December 2017.

2004-2008 Editorial board for "Developmental Brain Research".

Faculty of 1000, Cell Biology section, since 2003.

Reviewer for the following journals: Nature Cell Biology, Nature Genetics, Cerebral Cortex, Development, Journal of Neuroscience, Journal of Cell Biology, MCN, Traffic, and more. Grant reviews: Israeli Academy of Science, BSF, GIF, MRC, EU, ERC, DFG and more.

Awards and Honors

M.Sc. with honors.

1990, Feinberg graduate school prize in honor of Gad Reshef.

1990, Honor award to Ph.D. students by the Israeli Kneset.

1990, Haim Weizmann postdoctoral fellowship (declined)

1990, Fullbright award.

1990-1992, Human Science Frontiers Organization Long Term fellowship.

1993, Fogarty fellowship.

1994-2003, Incumbent of Aser Rothstein Career Development Chair in Genetic Diseases.

1994-1996, Recipient of Basil O'Connor Scholar Starter award from the March of Dimes.

2004-present, Incumbent of the Berstein-Mason professorial chair of Neurochemistry.

2008, Gruss Lipper Family Foundation Fellowship, summer 2008 MBL, Woods Hole, MA.

2009, Israel Cancer Association excellence award in memory of Prof. Daphna and Prof. Dov Izraeli.

2009, Gruss Lipper Family Foundation Fellowship, summer 2009 MBL, Woods Hole, MA.

2011, Henry Gutwirth Research Award.

2013, Neuroscience Center of Excellence, Chancellor's Award Lecture in Neuroscience.

DEVELOPMENTAL AND CELLULAR ASPECTS OF THE BRAIN

Orly Reiner

A scientific view of the developing embryonic cortex will be presented. Basic developmental, cellular and molecular aspects of the developing telencephalon will be introduced, starting from the early neuroepithelium to the formed cortex. The concepts of the signaling centers, the neural stem cell proliferation, the cell fate determination and neuronal migration will be discussed.

BRAIN ORGANOIDS FOR STUDYING NORMAL AND DISEASED BRAIN DEVELOPMENT

Orly Reiner

The origin of human brain wrinkling remains an open fundamental problem, with implications for neurodevelopmental disorders. One such example is lissencephaly, a condition in which the brain surface is lacking most of the typical convolutions. Despite multiple studies regarding the molecular and cellular functions of the LIS1 protein, the understanding of why the brains are smooth is still lacking. Physical organoids studies in polymer gel models suggest wrinkling emerge spontaneously due to development of compression forces during differential growth of cell layers. However biological evidence is limited. Here, we report the emergence of surface wrinkles during in vitro development of human brain, in a micro-fabricated compartment, which supports in situ imaging at a subcellular resolution over weeks. Gene expression studies demonstrate that these on-chip organoids express markers typical of early forebrain development. The folding dynamics and morphology exhibit similarity to folding in vivo. By studying the cellular dynamics, we observe nuclei compression during development and the emergence of convolutions at a critical cell density. We identify two opposing forces which contribute to differential growth: cytoskeleton contraction at the organoid core, and nuclear expansion during cell-cycle at the organoid perimeter. The wrinkling wavelength exhibits linear scaling with tissue thickness, consistent with polymer physics. Remarkably, lissencephalic (smooth brain) organoids exhibited reduced convulsions, linear scaling with an increased prefactor, and reduced elastic modulus. Furthermore, the lissencephalic organoids exhibited changes in gene expression in genes associated with the extracellular matrix. Our results support a physical mechanism for lissencephaly, in which changes in tissue elasticity result in reduced folding.

ZDRAVKO PETANJEK

Professor of Human Anatomy and Neuroscience, MD, Ph.D.
The University of Zagreb School of Medicine
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Education and academic career at School of Medicine (employed since 1992): 2016. Tenured Professor; 2013. Chairman of Dep. of Anatomy; 2007. Head of Zagreb Neuroembryological Collection; 1998. Head of Laboratory for Neuromorphometry. Participated in 20 research projects (head in 6). Author of 59 research articles, two chapters in scientific books and 60 congress/symposia proceedings, 26 invited lectures on scientific meetings. Cited more than 900 times, h factor 14. Mentor of 4 Ph.D., 2 Master, and 25 Graduate Theses. Founder of Laboratory for Computer Neuromorphometry and Confocal Microscopy at CIBR. Maintained more than 20.000 teaching hours on courses related with Anatomy, Neuroscience, Biological psychology, Neurology, and Psychiatry: participating in 20 graduate (head in 12) and 16 (head in 7) Ph.D. courses. Author of 2 textbook manuals, three teaching articles, 1 chapter in the textbook, translator of 2 textbooks and three chapters in textbooks.

Research interests: General research interest is to assess the organization of cortical circuitry via a multidisciplinary approach in human and animal models. Specific main interest is systematic quantitative research of (a) adult and developmental, morphological (re)organization of pyramidal neurons in the human prefrontal cortex, and (b) immunohistochemical studies about organization and origin of primate cortical calretinin GABAergic neurons. Another specific interest is research of (c) circuitry reorganization in human cortical pathology, in the experimental animal model, genetically manipulated animals and animals raised under the different environmental influence, as well as (d) comparative analysis of neuron morphology in various mammalian species.

Honors and Awards: 2014: Croatian Academy of Science and Arts, Award for extraordinary scientific discovery in the field of Medicine for the year 2013. 2011: School of Medicine University of Zagreb, Award for extraordinary scientific productivity; 1990: University of Zagreb Rector award for the best student scientific paper.; 1989: „Drago Perović“ award for the most valuable morphological discussion; 2001/2002 (2y) – “Post vert” fellowship, Marseille; 1994 (1y) – “Van den Houten” fellowship, Amsterdam

DANGEROUS TRIP FOR LEGAL IMMIGRANTS - CORTICAL GABAERGIC NEURONS: DISPERSED ORIGIN AND EXPANDED TIME WINDOW OF PRODUCTION

Zdravko Petanjek

During corticogenesis in mouse, the vast majority of cortical GABAergic neurons originate from molecularly and morphologically distinct regions of ventral telencephalon and migrate tangentially into the cerebral cortex. The medial ganglionic eminence (MGE) is a primary source: Nkx2.1 progenitors in the ventral part of MGE produce parvalbumin-expressing subpopulation, and Nkx6.2 co-expressing progenitors in the dorsal part of MGE produce somatostatin subpopulation. The second greatest source of GABAergic neurons is the caudal ganglionic eminence (CGE). Progenitors from the CGE express COUP-TF I/II and generate calretinin-positive cells. In monkey and human cerebral cortex, there is a considerable increase in the proportion and number of calretinin neurons that account for about 50% of the GABAergic population. Contrary to rodents, massive production of calretinin neurons occurs during the early fetal period in all parts of ventral telencephalon: MGE, CGE, and also LGE. The most dorsal part of the LGE (dLGE) produces mainly calretinin neurons for cerebral cortex, and not only for olfactory bulb and amygdala as is the case in rodents. After the early fetal stage, we observed a novel pool of GABAergic neuron progenitors in the pallial (cortical) proliferative zone that is suggested to produce mainly calretinin subpopulation. Dorsally derived GABAergic neurons migrate in non-radial direction, and neurons from the GE tangentially migrate via various streams located in the subventricular and intermediate zone. These neurons highly express the only GAD65, but there is also an important migratory population of neurons that highly express GAD67. GAD67 positive cells accumulate in the basal telencephalon and migrate through the marginal zone and the layer under the cortical plate. During the early fetal period, these cells originate from until now undescribed specific parts of the rostrodorsal and caudal part of the medial telencephalic wall while during the middle fetal period originate from the proliferative zone at the top of the temporal lobe from where they enter the marginal zone. The septal eminence, as well as part of diencephalic ventral proliferative zones, contributes to this migratory stream in which most of the neurons express somatostatin. Also, we found signs of important GABAergic neurons production during last trimester of gestation, both in the ventral and selective parts of dorsal proliferative zones *(Supported by Croatian Science Foundation Grant 5943).*

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Education: Medical Degree cum laude, University of Siena, Italy, 1981. Specialization in Pediatrics cum laude, University of Siena, Italy, 1985. PhD degree cum laude, Erasmus University of Rotterdam, NL, Dept. Cell Biology and Clinical Genetics, 1991. Specialization in Clinical Genetics, ErasmusMC Rotterdam, 2010.

Positions and Honors:

1985-1986 Consultant in Paediatrics, University of Siena.

1992-1996 Research Scientist at the Dept. Clinical Genetics, Erasmus University Rotterdam

1996- University Medical Specialist, Dept. Clinical Genetics, Erasmus MC, Rotterdam.

2009- Associate professor, Dept. Clinical Genetics, Erasmus MC, Rotterdam

1982 Award as distinguished Italian medical graduate student (national competition).

1994 Steven Hoogendijk Prize by the "Bataafsch Genootschap der Proefondervindelijke Wijsbegeerte".

1994- Member of the Bataafs Genootschap der Proefondervindelijke Wijsbegeerte

2007-2015 Chair of the "Werkgroep ter bestudering van de Somatische Oorzaak van Zwakzinnigheid".

2015-2018 Member of Raad Wetenschap & Innovatie, Dutch Federation of Medical Specialists.

Clinical expertise and teaching: Neurogenetics: developmental brain disorders, malformations of the brain cortex such as lissencephaly, polymicrogyria, heterotopia. Dysmorphology. Neurometabolic disorders.

Teaching in medical curriculum at the Erasmus MC (3rd year bachelor), and member of the ErasmusMC team in the medical specializations in clinical genetics. Supervisor of clinical genetics stage for residents in AVG medicine (Arts Verstandelijke Gehandicapten).

Leading investigator of the NFU-registered Expertise Center for Brain Malformation (ENCORE, http://www.erasmusmc.nl/encore/neurogenetica/).

Research interest: Focus is the genetic cause of malformation of the brain cortex, associated syndromes and perinatal cerebrovascular disorders connected to cerebral malformation. As research milestones, identification of the gene defects in following disorders: Salla disease (SLC17A5, OMIM 604369), SPG50 (AP4M1, OMIM 612936), microcephaly-epilepsy-diabetes syndrome (IER3IP1, OMIM 614231), POREN2, familial porencephaly type 2 (COL4A2, OMIM 614483), PMGYS (RTTN, OMIM 614833), EML1 linked Band Heterotopia (EML1, OMIM 600348), Pseudo-TORCH syndrome (USP18, OMIM 607057), syndromic brain malformation linked to INTS1 and INTS8 gene.

Chair of the European Network on Brain Malformation (wCOST Action, CA16118, www.cost.eu).

Co-author of about 140 articles in peer reviewed journals and 10 book chapters. Supervisor of 5 PhD doctoral students. Ongoing research projects: ErasmusMC Mrace #104673; ZonMW-TOP #91217045.

WHAT IS THE ROLE OF THE CLINICAL GENETICIST IN THE DIAGNOSIS OF PRENATAL MCD

Grazia M.S. Mancini

MCD are developmental disorders which can occur as result of genetic mutations or of disruptive events of a different kind.

A wide array of tests is nowadays available to support and confirm the genetic diagnosis.

The consequences and long term prognosis of MCD can be predicted according to the cause and the clinical course in the first post-natal years. However, due to the developmental phases, the imaging limitations and the type of MCD both, the suspicion diagnosis and prognosis are more challenging during the pregnancy.

The clinical geneticist assists in the search for an etiological diagnosis plays a major role in decisions about which test can be performed at which stage of the pregnancy and what is the relevance for the family. The clinical geneticist also absolves a bridge function between the laboratory specialist, the medical "organ" specialist (e.g. neurologist, gynecologist, pathologist etc.) and the family in interpreting, advising and explaining medical, social and psychological consequences of the genetic test.

During the talk tools, and mostly hints will be presented, which help us to suspect a genetic cause of brain malformation in the prenatal setting and eventually to request the appropriate test.

Taking examples from personal experiences and available literature, the hints can derive from:

1) Brain Ultrasound or MRI
2) Other congenital anomalies
3) The result of genetic screening
4) Examination of parents
5) Family history

After a review of the available genetic tests and their application during pregnancy, the pro's and contras of the prenatal testing will be analyzed and the value of the follow up after the pregnancy.

At the end of the presentation the participant will hopefully retain the following take-home message:

1) Early diagnosis of MCD during pregnancy is still difficult
2) It is important to combine information from different sources, not limited to fetal imaging
3) Beware of prognostic pitfalls when the etiological diagnosis is lacking
4) Brain disruption can be genetic
5) There are no genetic tests which exclude a genetic cause

PETER BAUER

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Germany
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Education

2010 Habilitation in Human Genetics, Eberhard-Karls-University Tübingen;

2006 Board Certification in Human Genetics Eberhard-Karls-University Tübingen;

1997 Thesis in Medicine Humboldt-University, Berlin;

04/1993 – 07/1997 Medicine Free University Berlin;

04/1990 – 03/1993

Medicine Albert-Ludwigs-Universität, Freiburg im Breisgau ;

10/1988 – 03/1990 Fine Arts Federal Academy of Fine Arts, University of Karlsruhe.

Profesional activities:

Since 01/2017 Chief Scientific Officer Centogene AG, Rostock;

01/2016 - 12/2016 Chief Operating Officer Centogene AG, Rostock;

08/2001 – 12/2015 Head of Molecular Genetics Institute of Medical Genetics and Applied Genomics, University of Tübingen;

09/1997 – 07/2001 Residency in Neurology Department of Neurology, University of Rostock.

Peter Bauer is a member of the executive board of CENTOGENE AG, Rostock (Germany) where he has continuously broadened the portfolio and increased the efficiency in diagnostic processes through implementation of high-throughput Next-Generation Sequencing (NGS). Besides large screening projects, where thousands of samples receive limited genotyping and biomarker profiling, he designed and implemented the diagnostic Whole Genome Sequencing workflow at CENTOGENE using the HiSeq X technology becoming the first European diagnostic provider in rare diseases. Since 2017, as Chief Scientific Officer, he focused on bioinformatics integration of genomics, transcriptomics and peptidomics for rare diseases and somatic cancer analysis. From 2001 to 2015, he has headed Molecular Genetics and the Core Facility for Applied Transcriptomics and Genomics, Institute of Medical Genetics and Applied Genomics, Tübingen. In diagnostics, he has established a broad portfolio of technologies and tests within the Institute focusing on neurodegenerative diseases, genetics of intellectual disability and cardiogenetics. The diagnostic laboratory uses all current molecular technologies including PCR / Sanger sequencing, MLPA, real-time PCR, SNP array diagnostics, and next-generation sequencing making the Institute of Medical Genetics and Applied Genomics a highly visible academic supplier of cutting-edge molecular genetic testing.He still holds a teaching and research position at the Institute of Medical Genetics and Applied Genomics in Tübingen.

Research interest lies on the genomic analysis and diagnostics of neurodegenerative diseases, where he has authored more than 150 peer-reviewed publications. He is a partner in several European networks dealing with the implementation of NGS in clinical practice (EMQN, TECHGENE, ad-hoc commission for genetic testing of the German Society of Human Genetics). Furthermore, he is committed to Next-Generation-Sequencing diagnostics and developing NGS guidelines. He has broad experience in Next-Generation-Sequencing application both in research and diagnostics.

THE INPUT OF NGS TECHNOLOGY ON THE DIAGNOSIS OF BRAIN MALFORMATION AND IDENTIFICATION OF NOVEL GENES

Peter Bauer

Next-Generation Sequencing has exhibited tremendous impact on rare disease research and diagnostics. While standard diagnostics in brain malformation rarely went beyond lisencephaly or very few leucencaphopathic syndromes, gene panel sequence, whole exome sequencing, and even whole genome sequencing are more and more used to diagnose patients with typical symptoms and discover new rare and ultra-rare disease genes. The presentation will give an introduction to next-generation sequencing and a variety of parameters defining the sensitivity and the specificity of the technology. Even more importantly, the clinical utility of NGS diagnostics will be defined for rare diseases and brain malformations in particular. The talk will highlight the tight interaction of accurate phenotyping and appropriate variant classification and interpretation as well as the integration of validation tools to deal with many variants of uncertain clinical significance that show up in the sequencing process. As a result, besides the framework of NGS diagnostics, students will be able to evaluate critical quality parameters of NGS assay formats and how to put this information into the context of their research or clinical work.

ANDREW E. FRY

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Education:

1997	BSc. (Hons) in Molecular Biology, 1st Class, University of Glasgow
2000	MB.ChB. with Honours, University of Glasgow
2004	Member of the Royal College of Paediatrics and Child Health
2009	D.Phil., University of Oxford
2014	Certificate of Completion of Training (Clinical Genetics)

Professional activities:

2017-present	Clinical Senior Lecturer in Medical Genetics / Cardiff University
2015-2017	Clinical Research Fellow in Medical Genetics / Cardiff University
2010-2014	Clinical Lecturer in Medical Genetics / All Wales Medical Genetics Service
2007-2010	Academic Clinical Fellow / All Wales Medical Genetics Service
2004-2007	Clinical Research Training Fellow / University of Oxford
2001-2004	Paediatric Senior House Officer / London/ Maidstone
2000-2001	Pre-registration House Officer / Glasgow/ Paisley

Research interests: the genetic basis of malformations of cortical development (particularly polymicrogyria) and severe early-onset epilepsies.

POLYMICROGYRIA – CLINICAL AND MOLECULAR CONSIDERATIONS

Andrew Fry

Polymicrogyria (PMG) is a heterogeneous malformation of cortical brain development.

Symptoms of PMG depend on the distribution and extent of the affected cortex but often include developmental delay, intellectual disability, spasticity, muscle weakness, and seizures. Diagnosis is typically made by brain MRI that reveals either irregularity to the cortical surface suggestive of multiple small folds or blurring of the gray matter-white matter junction. The etiology of PMG is complex and includes both environmental (vascular events, congenital infection) and genetic factors. We recruited a cohort of 121 PMG patients. The cohort comprised 99 single probands (with no other affected family members) and 22 PMG patients from 10 families. We reviewed the clinical features, examination findings, MRI images and previous investigations for each patient. All participants were tested by SNP array if an NHS array had not previously been performed. We found the frequency of pathogenic or possibly-contributory CNVs was relatively low among PMG patients. We then exome sequenced members of 10 families, 57 proband-parent trios, and four individual probands. Genes hit more than once by pathogenic de novo point mutations included TUBA1A, PIK3R2, and GRIN1. We identified single de novo hits in other known PMG genes and several genes with biologically-relevant functions. Overall, our results highlight the clinical and genetic heterogeneity of PMG.

MAHA S. ZAKI

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Education: Graduated from Cairo University in 1984. Attached to National Research Centre, Genetics Department in 1986; Master degree in Pediatrics at 1991, Ph.D. in Pediatrics in 1998. Professor of Clinical Genetics since 2009; Head of Clinical Genetics Department in NRC since 2016.

Professional activities Founder the Neurogenetics clinic, Medical Services Unit, NRC since 2004, and the Neurogenetics clinic in National Institute of Neuromotor system, Ministry of Health since 2001. Participating in many national and international projects as principal investigator, co-principal investigator, and researcher, Maha Zaki, established many collaborations with Europe and USA. Supervising many Master and Ph.D. theses in the department and universities, published about 110 publications mostly in international journals and some were in very high impact factor journals such as Nature Genetics, Science, Cell, AJMG, Neurology, Annals Neurology, and Brain. Participated in the discovery of many new genes in Joubert syndrome, microcephaly, cerebellar atrophy and mental retardation. Delineated new recessive syndromes and assigned a new developmental brain defect, published in Brain. Member in ESHG, ASHG, SIEM, SPATAX network (A worldwide international network on hereditary ataxia and spastic paraplegia) and many national organizations.

Research interest: Neurogenetics, Developmental brain defects, and Clinical Genetics.

Awards: Won The National prize of Science Excellency in Science and Advanced Technology for 2011. Won several prizes for publishing in high impact factor journal and for many scientific activities from organizations in Egypt and NRC.

MIDBRAIN AND HINDBRAIN ANOMALIES

Maha Zaki

Midbrain and hindbrain (MB-HB) anomalies are an emerging group of developmental disorders with a significant implication of neurodevelopmental dysfunction including intellectual, behavioral and motor disabilities. Each has a unique clinical presentation and a specific neuroimaging characterization. A basic understanding of MB-HB development and its genetic background are essential for better understanding of these malformations. MB-HB anomalies could be associated with supratentorial malformations due to the similar process occurring in both forebrain and hindbrain as in cobblestone malformations, or associated with lissencephaly as in RELN pathway or microtubule function (tubulinopathies). MB-HB anomalies can be broadly classified as predominantly involving the cerebellum as in Dandy-Walker malformation, cerebellar hyperplasia, hypoplasia or dysplasia and rhobencephalosynapsis. Both cerebellum and brain stem malformations are in pontocerebellar hypoplasia (PCH), Joubert syndrome and related disorders (JSRD), pontine tegmental cap dysplasia (PTCD) and congenital disorder of glycosylation. Predominantly brain stem malformations are in congenital cranial dysinnervation disorders which are either without neuroimaging findings or with specific butterfly shape of brain stem as in horizontal gaze palsy with progressive scoliosis (HGPPS). A recently assigned anomaly that predominantly affected the midbrain is a fusion of diencephalon and mesencephalon that leads to diencephalic mesencephalic junction defects (DMJD). Clinical Classification of MBHB disorders is important in providing a better understanding for accurate diagnosis and targeting genetic testing aiming for identifiable prognosis, genetic counseling and prenatal and carrier testing.

HÜLYA KAYSERİLİ

Professor, MD, Ph.D.

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Education: Medical Degree, Istanbul Medical School, İstanbul University, 1984. Specialization in Family Medicine, Şisli Etfal State Hospital, İstanbul, Turkey, 1991. Faculty of Letters, Classical Archeology Division, Istanbul University, Turkey,1989. PhD degree on Genetics, Institute of Child Health, Institute of Health Sciences, Istanbul University, Turkey, 1998.

Academic and Professional Experience

- 02.2015-ongoing, Prof. Full time faculty, Head of Medical Genetics Department, Koç University School of Medicine (KUSOM) İstanbul, Turkey
- 12.2009-02. 2015, Prof. Lecturer; Clinical Genetics & Pediatric Genetics Division, Medical Genetics Department, Lecturer at Institute of Health Sciences, Istanbul University, Turkey
- 03.2004-12.2009, Assoc. Prof. Lecturer; Chief of Clinical Genetics Division, Medical Genetics

Department, Istanbul University, Turkey

- 05. 1992-03.2004, Specialist, PhD student, post doc; Prenatal Diagnosis and Research Center &

  Institute of Child Health, Division of Medical Genetics, Istanbul University

  Short term visiting fellowships, Cedar Sinai Hospital, Genetics Dept., UCLA, LA, USA & Medical Genetics & Pediatric Genetics Department, Academic Medisch Centrum, Amsterdam, & Genetics Research Laboratory, Free University, Amsterdam, the Netherlands

Clinical expertise and teaching

- Clinical and molecular syndromology; dysmorphology; developmental genetics
- Genetics of intellectual disability & autism & neurogenetics
- Prenatal genetics & fetal pathology
- Clinical research & research on novel treatment modalities
- Teaching in medical curriculum at Koç University Medical school (2nd, 3rd, 4th year) and Institute of Health Sciences, Cellular and Molecular Medicine PhD program

Research interest

Etiopathogenesis of rare craniofacial dysmorphic syndromes and limb malformations. Frontonasal dysplasias and Moebius syndrome has been the main focus of her studies since 2008, through CRANIRARE and CRANIRARE2 consortiums [E-Rare (ERA-Net for research programs for rare diseases) network supported by European Commission under the Seventh Framework Program]. She has clinically delineated new syndromes, and works on the classifications of known phenotypes, on the identification of the gene/s involved, on functional assays to elucidate various signaling/metabolic pathways and crosstalks. Rare neuromuscular and neurogenetic disorders are among her research topics, in view of the expanding new technologies, gene-editing, leading to the tailor-made treatment models for single gene disorders in the new era of translational genetics. MC member of the European Network on Brain Malformation (COST Action, CA16118, www.cost.eu). Co-author of about 200 articles in peer reviewed journals and 12 book chapters.

CLINICAL DYSMORPHOLOGIST APPROACH TO SYNDROMIC MCD

Hülya Kayserili

MdMalformations of cortical development (MCD) involve a rare group of disorders, and the etiopathogenesis is heterogeneous. In a limited number of the entities, the etiopathogenesis is syndromic, and dysmophologists' evaluation may lead to a prompt diagnosis.

Gestalt diagnosis is the well-known approach for dymorphologists, and it is also applicable for some syndromic MCDs. As the clinician gains more expertise, she/he feels more confident to pinpoint the test relevant to the clinical diagnosis although may experience the pitfall of misdiagnosis.

The best diagnostic strategy for rare syndromes is the combination of by-the-book, classic, so-called the Scotland Yard Model and Dr. Watson pattern recognition model. The diagnostic process begins with detailed and complete medical history and a meticulous physical examination as in Scotland Yard model and the pattern recognition ability of the diagnostician as in Dr. Watson model. The clues from medical history and physical examination are the pivotal features leading to definite diagnosis. In this approach, the best clinical handles leading to the diagnosis should be chosen by the dysmorphologist. The hair-to-toe detailed examination is a must, and universally accepted method for dysmorphic evaluation.

The presentation will cover gestalt diagnosis in some syndromic MCDs and the clinical handles leading to definite diagnosis such as focal alopecia, midline hemangioma of the face, hemihypertrophy, 2-3 toe syndactyly and combinations of some other minor anomalies, spectrum variants.

The success and the diagnostic pitfalls (confessions) of dymorphologists' clinical approach will be discussed along with case presentations.

GUSTAVO MALINGER

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Tel Aviv Sourasky Medical Center,
Sackler School of Medicine,
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Education: Born in Montevideo, Uruguay, Gustavo Malinger, MD, traveled to the opposite side of the globe for his education, where he studied at Hebrew University Hadassah Medical School and earned his medical degree from the Sackler School of Medicine, Tel Aviv University. He subsequently completed his residency in Obstetrics and Gynecology at the Edith Wolfson Medical Center (WMC), where he also served as a lecturer and as a tutor in surgical technique. He was Visiting Scientist at The Weizmann Institute of Science. Israel; Senior Consultant at Postgraduate Medical Program, University of Hawai, Okinawa, Japan and visiting Professor at the Department of Neuroradiology, Allgemaine Krankenhaus, Vienna, Austria.

Profesional activities: From 1994 until 2012, he was director of the Prenatal Diagnosis Division and co-director of the Fetal Neurology Clinic at WMC. Since 2013, Professor Malinger has been director of the Obstetric and Gynecologic Ultrasound Division at Lis Maternity Hospital—the OB-GYN facility of Tel Aviv Sourasky Medical Center. Known worldwide for his research on the fetal brain, Professor Malinger has published close to 150 manuscripts and book chapters, including the first descriptions of fetuses with congenital Zika virus syndrome. His most recent book, Ultrasonography of the Prenatal Brain, was completed in collaboration with Ilan Timor-Tritsch, MD, FAIUM, Ana Monteagudo, MD, RDMS, FAIUM, and Gianluigi Pilu, MD, FAIUM (hon), and published in 2012. An associate clinical professor at the Sackler School of Medicine, Professor Malinger has been a strong proponent of education since his medical school days. Not only has he presented more than 300 lectures at meetings in Israel, the United States, Europe, Asia and South America, he has served as a course director, symposium director, or congress director for organizations around the world ranging from the Israeli Society of Ultrasound to the First Israeli Congress on Fetal Neurology to multiple World Congresses of Ultrasound in Obstetrics and Gynecology to various "Advanced Courses" for the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG). Professor Malinger has served as an external expert on reproductive health and research for the World Health Organization and has supervised the work of 3 doctoral candidates and five students earning their master's degrees. A reviewer for 16 medical journals and member of the Editorial Board of Ultrasound in Obstetrics and Gynecology, Professor Malinger is active in a dozen medical associations throughout the world.

Areas of interest: Fetal brain imaging, fetal infections, and insults, new technologies in fetal medicine, 1st, 2nd and 3rd-trimester screening.

Awards: Both the Chilean Society of Ultrasound in Medicine and Biology and the Argentinean Society of Ultrasound in Medicine and Biology have granted him honorary membership status. The American Institute of Ultrasound in Medicine added recently one more additional honorary membership to this physician's impressive curriculum vitae.

EARLY PRENATAL ULTRASONOGRAPHIC FINDINGS SUGGESTIVE OF MALFORMATIONS OF CORTICAL DEVELOPMENT

Gustavo Malinger

Abnormal neurodevelopmental events leading to malformations of cortical development (MCD) occur during the 2nd and 3rd trimesters and usually remain undetected until close to or after delivery. Using high definition ultrasound, we are currently able to study normal lamination and cortical development, starting at 14 weeks of pregnancy and at the same time to identify in some cases, probably representing the most severe side of the spectrum, signs of abnormal development of these structures. These sonographic findings including callosal anomalies; the presence of an abnormal ventricular wall; abnormal overdeveloped or non-developed sulci; and disruption of the normal cortical pattern appear as diagnostic or highly suggestive of MCDs and may be visualized between 14-24 weeks of gestation. In most of these patients, the presence of associated anomalies facilitated the diagnosis. When using an adequate technique, familiarity with fetal brain anatomy and its early sonographic landmarks allows early diagnosis of severe cases of MCDs.

MAARTEN LEQUIN

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Record of research achievement: Maarten Lequin, heads both clinical radiology and radiological research in the largest hospital specializing in pediatric care and pediatric oncology in the Netherlands -- Wilhelmina Children's Hospital and Princess Maxima Center in Utrecht. His Ph.D. dissertation "Tibial ultrasonometry in children" was honored by the Dutch Osteoporosis Foundation in 2001, the Symen Duursma price

Dr. Lequin's research has gained new impetus following a 6-month fellowship in pediatric neuroradiology with Jim Barkovich, Chief of Neuroradiology at the University of California at San Francisco, CA, USA, one of the founding fathers of pediatric neuroradiology. This research line is devoted to neuroimaging of the premature and neonatal brain and has already been honored with a grant from the Beatrix Fonds.

He has organized the European Course on Pediatric Radiology in Rotterdam in 2013 and co-organized the European Society Meeting in Amsterdam in 2014.

In the course of his career, Dr. Lequin has published over 200 articles (*h*-index 35), in leading international journals including many articles on neuroimaging. He has authored many chapters in medical textbooks and taught a special course on pediatric neuroradiology at the invitation of the Ministry of Health of the Republic of Peru (*Ministerio de Salud, region de Salud Arequipa Hospital Goyeneche Cuerpo Medico*). He has continuing collaborations with world-known pediatric neuroradiologists, like Prof. Jim Barkovich at UCSF, and Prof. Thierry Huisman, head of Radiology Johns Hopkins, Baltimore. He is a member of the pediatric board of the Dutch Society of Radiology, a member of the European Society of Pediatric Radiology, and an honorary lifetime member of the Society of Peruvian Radiologists (*Sociedad sur Peruana de Radiologica*).

He was co-promotor for several thesis projects focused on pediatric neuroimaging.

Since 2017 he is the leader of the imaging workgroup of the COST project, focusing on malformations of cortical development.

MALFORMATIONS OF CORTICAL DEVELOPMENT

Maarten Lequin

Malformations of cortical development (MCD) are an ultra-rare group of disorders but constitute a major cause of lifelong intellectual and motor disability and epilepsy. The etiology is heterogeneous (genetic, infectious, toxic, etc.). The brain abnormalities are discovered on brain scans, mostly MRI, during childhood in most affected individuals. MCD are characterized by an abnormal structure (micro- or macroscopic) of the cortex. The first classification based on imaging was introduced by Barkovich 1996 and in the following years up-dated (Barkovich et al., 2001; 2005; 2012; Desikan and Barkovich, 2016). All these classifications are focused on the concept that the development of the cortex is divided into three major stages (Abdel Razek et al., 2009; Bystron et al., 2008): cell proliferation and apoptosis, cell migration, and finally post-migrational development. These different processes take place at different times in different parts of the brain, so many parts of the different processes occur at the same time. The proliferation of neurons in the dorsal telencephalon of the human fetus starts around the 6th gestational week (gw) decreases after 16 gw and finishes around 22-25 gw. During the presentation, the focus will be on cases to illustrate this concept of three stages of development.

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NATALIYA DI DONATO

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Education:

05/2010 Human Genetics Board Examination

09/2005 – 05/2010 Fellowship at Human Genetics, at the Institute for Medical Genetics, Zürich, Switzerland and Institute for Clinical Genetics, TU Dresden, Germany

07/2002- 12/2004 Master program in Medical Genetics, Department of Human Genetics, Medical Academy, Kiev, Ukraine

09/1996 – 06/2002 Study Medicine, Medical University of Kharkiv, Ukraine

Scientific degrees:

12/2017 Habilitation thesis "Malformations of Cortical Development - genetics and pathomechanisms", Institute for Clinical Genetics, Faculty of Medicine CGC, TU Dresden, Germany (Prof. Dr. Evelin Schrock)

09/2005 – 05/2007 MD PhD-thesis "Identification of candidate gene loci for congenital brain defects with the help of unbalanced chromosome aberrations" Institute for Medical Genetics, University of Zürich, Switzerland (Prof. Dr. Albert Schinzel)

Academic and research appointments:

11/2015 – present Group leader, Institute for Clinical Genetics, TU Dresden

09/2014 – 10/2015 DFG Research Fellowship Grant

Research postdoctoral fellow, Dobyns Lab, Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, USA

06/2011 – 09/2014 Head of the Genetic Counselling Department, Institute for Clinical Genetics, TU Dresden

01/2007 – 05/2011 Board-certified medical geneticist (before medical fellow) and research associate Institute for Clinical Genetics, TU Dresden

09/2007 – 12/2006 Swiss Government Awards University Scholarship, Ph.D. Student, and Medical Fellow, Institute for Medical Genetics, University of Zürich, Switzerland

07/2002 – 08/2005 Fellow at the Department of Human Genetics, Medical Academy of Postgraduate Education and Amosov National Institute of Cardiovascular Surgery, Kiev, Ukraine

LISSENCEPHALY: MOLECULAR DIAGNOSTICS, MANAGEMENT AND COUNSELING

Nataliya Di Donato

Lissencephaly ("smooth brain" LIS) is a malformation of cortical development associated with deficient neuronal migration and abnormal formation of cerebral convolutions or gyri.

The LIS spectrum includes agyria, pachygyria, and subcortical band heterotopia. This talk will introduce a novel imaging-based classification system with 21 recognizable patterns that reliably predict the most likely causative genes. Recognition of one of these imaging patterns can support analysis of the many variants of unknown significance associated with genetic testing. Further, the genetic testing results (even when negative) and brain-imaging pattern combine to robustly predict both the most likely patterns of inheritance as well as the most likely clinical outcome, making them important for clinical management of patients. We will also discuss a newly developed diagnostic testing strategy provides a robust pipeline for both medical professionals with no special skills in MRI interpretation as well as specialists with substantial expertise.

Additionally, a current clinical implication of the knowledge of the underlying genetic cause will be summarized.

RENZO GUERRINI

Professor of Child Neurology and Psychiatry, MD
Director of the Neuroscience Department
Director of the Pediatric Neurology Unit
Laboratories at Children's Hospital Anna Meyer
University of Florence, Florence, Italy

Professional activities and previous appointments: Professor of Clinical Neuroscience – Epilepsy, Director of the Centre for Epilepsy at King's College University of London UK; Professor of Pediatric Neurology at the Institute of Child Health and Great Hormond Street Hospital, University College London UK; Professor of Child Neurology and Psychiatry and Research Director at the Child Neuropsychiatry Research Institute University of Pisa Italy.

Prof. Guerrini has authored over 500 Articles in peer-reviewed journals, edited or authored 12 books on epilepsy and given over 400 invited lectures throughout the world. He has served in the Editorial board of several journals and book series including Neurology, the Journal of Child Neurology, Epilepsia, Epileptic Disorders, Seizure, Neuropediatrics, Neurological Sciences, European Journal of Neurology, BMC Medical Genetics, Progress in Epileptic Disorders, Topics in Epilepsy, and has served as an Associate Editor for Epilepsia from 2006 to 2013. He has chaired the Commission on Pediatrics of the International League Against Epilepsy and participated to other ILAE commissions and task forces and to committees and commissions on Pediatric Epilepsy for the World Health Organization, the European Medicines Agency, and the INSERM. He was awarded the Ambassador for Epilepsy ILAE recognition in 2003, the Award for Research in Clinical Science by the American Epilepsy Society in 2012 and is a Fellow of the Royal College of Physicians (London).

Prof. Guerrini has been the principal investigator of numerous research project funded by the Italian Ministry of Health and Research, by the EU and by Telethon, on the genetics of the malformations of cortical development, and the neurobiology and genetics of epilepsy. He is now Coordinating DESIRE (Development and Epilepsy - Strategies for Innovative Research to improve diagnosis, prevention, and treatment in children with difficult to treat Epilepsy), a major EU Research project funded by the 7th framework program. His research activities have coupled the classical clinical epileptology based on observation and semiology with the more modern diagnostic methods and laboratory-based research. With his research activities, Prof. Guerrini has made important contributions in characterizing the clinical phenotype and the genetic causes of various epilepsy or brain malformation syndromes and defining genotype-phenotype correlations. His work has been instrumental in improving diagnostic and treatment strategies and to set the basic science framework for experimental analysis in animal models.

MALFORMATIONS OF CORTICAL DEVELOPMENT AND HUMAN PHENOTYPES: DIRECTIONS FOR RESEARCH

Renzo Guerrini

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Professional activities: child Neurologist conducting the rare disease program on Rett syndrome and brain malformation at Necker Enfants Malades University Hospital, APHP, Paris. She is also conducting research works in the Imagine Institute - INSERM UMR-1163 in A Pierani team, on Genetics and Pathophysiology of brain malformations Paris Descartes University

2017: Contrat d'interface INSERM in the team of Alessandra Pierani. Institut Imagine

2016: Full Professor (PUPH), Pediatric Neurology, Necker Enfants Malades university hospital, APHP

2011: Research Director Accreditation ("Habilitation à Diriger des Recherches")

2005: Ph.D. degree, Paris VI University, in Ecole Doctorale Cerveau-Cognition-Comportement (ED 3C) Neuroscience

2000 – 2002: Ph.D. student under the direction of Jamel Chelly. Inserm U106 and Institut Cochin - Paris, France.

2000: Gold medal at the competitive residency examination, 2000

1999: Certified by the Board of Paediatrics

1999: Medical Doctorate (Paris V University)

1996 Masters in "Neurosciences " ("Diplôme d'Etudes Approfondies"). (Department head: Prof. Pierre Gressens INSERM UMR_S1141)

1994 - 1999: Residency in the Assistance Publique - Hôpitaux de Paris Teaching Hospital network

1994: Masters of Biological and Medical Science, in molecular biology and immunology (Paris V University)

Scientific summary: She is a part of the group "Genetics and Cerebral cortex development" (A Pierani) of the Imagine Institute (INSERMU1163 directed by Stanislas Lyonnet), interested in understanding the cellular and molecular mechanisms of brain development, especially neurogenesis, and neuronal migration. The main goal is to understand the molecular basis of Malformations of Cortical Development which are important causes of intellectual disability and account for 20-40% of drug-resistant childhood epilepsy. The group conducts integrated multidisciplinary studies involving cellular and molecular biologists, fetal pathologists and radiologists, using a wide range of approaches including genetics, biochemistry, and cellular biology to better understand the signaling pathways involved in these processes and how their dysregulations can lead to pathologies. As a medical doctor and a researcher, she established collaborations with clinicians and geneticists providing a transversal appreciation of the researchers.

The main subjects of the project are: [1] the identification of new genes and molecular actors involved in normal migration processes and being altered on MCDs; [2] a better understanding of the link between genotype and phenotype, and of the process leading to an abnormal migration pattern;

Past and recent works:

- Role of DYNCH1 in the brain malformations and spinal muscular atrophy
- Stem cells and mechanisms contributing to human cortical malformations
- Development and differentiation of patient-derived iPSCs, correcting FOXG1 loss-of-function

THE PHENOTYPIC SPECTRUM OF DYNEINOPATHIES: FROM LISSENCEPHALY TO SPINAL MUSCULAR ATROPHY WITH LOWER LIMB PREDOMINANCE

Nadia Bahi Buisson

The development of the cortex, responsible for our complex cognitive capacities, occurs via a highly regulated sequence of events, involving proliferation in zones close to the ventricles, followed by long-range migration of newborn neurons to establish the highly ordered cortical neuronal layers. Perturbations of these steps can lead to a variety of cortical malformations (MCD), crudely classified according to the earliest developmental step at which the developmental process was disturbed,and updated recently. Genetic approaches in combination with fetal and post-natal brain magnetic resonance imaging (MRI), or post-mortem studies, continually allow a re-evaluation and a better classification of these disorders. Our groups have contributed to this work, providing significant data concerning molecular mechanisms involved in cortical development. Mutations in genes such as LIS1, DCX (doublecortin), TUBA1A and recently DYNC1H1 are implicated in more than 60% of lissencephaly spectrum cases. We are particularly interested here, in these genetic disorders, involving genes coding for microtubule (MT) or neuronal transport components.

Over the past years, cytoplasmic dynein 1 (hereafter dynein) has emerged as a key player in neocortical neurogenesis and migration. In humans, dynein is responsible for a wide variety of cellular functions such as the movement of organelles, transport of vesicles, proteins and mRNA during interphase, maintenance of the Golgi apparatus, and en-

dosome recycling. It is also involved in numerous aspects of mitosis, including mitotic spindle organization and orientation, interactions of kinetochores with MTs, and mitotic checkpoint regulation. Cytoplasmic dynein also has neuron-specific functions and is particularly involved in neuronal migration, retrograde axonal transport and polarized trafficking into dendrites.

In 2010, the first human DYNC1H1 mutation was found in an individual with developmental delay, hypotonia and MCDs. In parallel, DYNC1H1 mutations were reported in various neurodevelopmental and neurodegenerative diseases affecting either both motor and sensory neurons, including dominant hereditary distal motor Charcot Marie Tooth (CMT) type 2, or motor neurons with lower extremity-predominant spinal muscular atrophy-1 (SMA-LED). The key clinical features in individuals with these DYNC1H1 related neuropathies is their congenital occurrence or very early-onset weakness in proximal parts of legs and a static or mildly progressive disease course. We refer to these neuropathies, as "peripheral" dyneinopathies.

Later on, we and others, reported new de novo point mutations in DYNC1H1 using exome and Sanger sequencing in individuals (mostly sporadic cases) diagnosed with a wide spectrum of MCDs ranging from the lissencephaly spectrum (from agyria pachygyria to band heterotopia) to polymicrogyria (PMG) with or without microcephaly. Importantly, they represent a major cause, probably the second most important cause of lissencephaly after LIS1 mutations (personal data).

This presentation will be dedicated on the presentation of the wide spectrum of dyneinopathies and the comparison with other cytoskeleton and MAP related cortical malformations.

MILOŠ JUDAŠ

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CORTICAL CHANGES IN HOLOPROSENCEPHALY AND WALKER – WARBURG LISSENCEPHALY

Miloš Judaš

Holoprosencephaly (HPE) is one of the most common human developmental brain malformations and is often associated with motor deficits, seizures, and mental retardation. The HPE is characterized by inadequate separation of cerebral hemispheres due to abnormal embryonic development of the forebrain midline. HPE cases are classified, in order of increasing severity, as lobar, semilobar, or alobar. However, the majority of HPE brains also exhibit a spectrum of defects (ranging from moderately affected to severely hypoplastic) in the development and midline separation of ventral forebrain structures, including the striatum. In the first Golgi study of the developing neocortex in the newborn with semilobar holoprosencephaly (Judaš et al. 2003), we found that the HPE neocortex retained its basic six-layered lamination but displayed some intralaminar and modular architectonic alterations and contained a mixture of normal and aberrant neuronal phenotypes. The most conspicuous finding was the presence of the pronounced increase in soma size and the dramatic (5-fold) dendritic overgrowth in layer III pyramidal neurons in comparison to age-matched control brains. We suggested that this dendritic overgrowth is probably related to the pronounced diminution of the cortical afferent input in the HPE. In another study, performed in collaboration with the group of Dr. Nenad Šestan at the Yale University School of Medicine (Fertuzinhos et al. 2009), we demonstrated that cortical interneurons expressing nitric oxide synthase 1 (NOS1), neuropeptide Y (NPY) and somatostatin are either absent or substantially reduced in fetal and infant cases of human HPE with severe ventral forebrain hypoplasia. In contrast, calretinin-positive interneuron subtype, as well as different subtypes of projection neurons were present in the cortex of control and HPE brains. These findings have important implications not only for the understanding of neuronal pathogenesis underlying the clinical manifestations associated with HPE but also for understanding the developmental origins of human cortical interneuron diversity. Namely, these findings demonstrate that the diversity of human cortical interneurons is established early during neurogenesis, with distinct subpopulations originating from spatially, temporally, and molecularly segregated pools of progenitors.

The Walker-Warburg syndrome (WWS) is a rare form of lissencephaly which occurs as an autosomal recessive disease. At present, the diagnosis of WWS is based on the presence of four major findings: (1) the presence of congenital muscular dystrophy with hypoglycosylation of alpha-dystroglycan, (2) increased blood levels of creatine kinase, (3) the presence of ocular abnormalities in the anterior or posterior eye chamber, and (4) the disturbed neuronal migration resulting in cobblestone lissencephaly with concomitant hydrocephalus and abnormal development of cerebellum and brain stem. In a recent study (Judaš et al. 2009), we analyzed the morphology and dendritic development of neocortical neurons in a 2.5-month-old infant with WWS homozygotic for a novel POMT1 gene mutation. We found that pyramidal neurons frequently displayed abnormal (oblique, horizontal, or inverted) orientation and that members of the same population of pyramidal neurons display different stages of development of their dendritic arborizations. For example, some neurons had poorly developed dendrites and thus resembled pyramidal neurons of the late fetal cortex; for some neurons, the level of differentiation corresponded to that in the newborn cortex; and some neurons had quite elaborate dendritic trees as expected for the cortex of 2.5-month-old infant. Also, apical dendrites of many pyramidal neurons were conspicuously bent to one side, irrespective of the general orientation of the pyramidal neuron. These findings suggest that WWS is characterized by two hitherto unnoticed pathogenetic changes in the cerebral cortex: (1) heterochronic decoupling of dendritic maturation within the same neuronal population (with some members significantly lagging behind the normal maturational schedule) and (2) anisotropically distorted shaping of dendritic trees, probably caused by patchy displacement of molecular guidance cues for dendrites in the malformed cortex.

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GENOMICS AND IMAGING OF MALFORMATIONS OF BRAIN DEVELOPMENT

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TRAINEES' ABSTRACTS

FUNCTIONAL DISSECTION OF THE ENHANCER NETWORK IN NEURAL STEM CELLS AND BRAIN ORGANOIDS

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Enhancers are genetic elements that direct correct spatiotemporal regulation of gene-expression and are often predicted by co-localization of transcription factors (TFs) and enhancer-associated histone-modifications (e.g. H3K27ac, H3K4me1/3). Only a limited number of putative enhancers identified can be experimentally validated, indicating that current-state-of-the-art methods to identify functional enhancers have limitations. To identify functional enhancers quantitatively in a genome-wide manner, we have developed a new high-throughput screen, which combines chromatin-immunoprecipitation for TFs or histone modifications, with a massively-parallel-reporter-assay. Non-coding DNA sequences bound by TFs or marked by histone-modifications are cloned en masse in reporter plasmid libraries, which can be used in cell-transfection experiments, where enhancer-activity of cloned sequences can be quantified by RNA-seq. Using this ChIP-STARR-seq approach, we can directly functionally assess enhancer-activity of non-coding sequences at an unprecedented scale. We have previously applied this ChIP-STARR-seq approach to decipher the gene-regulatory network in human embryonic stem cells. Using this approach, we have identified approximately 20,000 highly active enhancers in that cell type, gaining novel insights on the regulation of gene expression in this clinical relevant cell type. Here we report on our ongoing efforts to identify functional enhancers involved in brain development. To this end, we are using several approaches, including massively-parallel reporter based assays, ChIP-seq, RNA-seq and chromatin conformation assays. Together, these assays should lead to a detailed map of functional enhancers involved in brain development, that might be targeted for mutations in unexplained patients suffering from neurodevelopmental disorders. The long-term goal is to develop novel diagnostic approaches that are of benefit for patients suffering from malformations of cortical development.

TUBULINOPATHIES CONTINUED: REFINING THE PHENOTYPIC SPECTRUM ASSOCIATED WITH VARIANTS IN TUBG1

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A heterogeneous group of malformations of cortical development with a wide spectrum of clinical severity is caused by variants in genes belonging to the tubulin superfamily. Among them, TUBG1 has previously been described in three patients with posterior predominant pachygyria and microcephaly.

With the use of gene panel analysis or whole exome sequencing four novel variants in TUBG1 in 8 additional patients could be identified. All had severe motor and cognitive impairment and all except one developed seizure in early life. The core imaging features included a pachygyric cortex with posterior to the anterior gradient, enlarged lateral ventricles most pronounced over the posterior horns, and variable degrees of reduced white matter volume.

The imaging phenotype associated with variants in TUBG1 with posterior predominant pachygyria differs from dysgyria described in variants of other tubulin genes and is more in line with the phenotype resulting from variants in LIS1 (a.k.a. PAFAH1B1). Basal ganglia, corpus callosum, brainstem, and cerebellum were often normal in patients with TUBG1 variants, while malformations in these structures are frequently observed in patients with variants in other tubulin genes. This difference may, at least in part, be explained by gamma tubulin's physiological function in microtubule nucleation, which differs from alpha and beta tubulins role in the microtubule lattice. Reduced protein function of TUBG1 can lead to changes in cell morphology causing reduced proliferation and under migration, ultimately leading to microcephaly and pachygyria.

ECM EXPRESSION PATTERN IN THE FETAL HUMAN CINGULATE GYRUS AND ITS RELEVANCE IN MALFORMATIONS OF CORTICAL DEVELOPMENT

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A complex system of the cingulate gyrus connections with other brain regions, underlie some malformations of cortical development (MCD) such as autism and epilepsy. Quantity and composition of ECM of the transient developmental zones of the human fetal brain play a crucial role during cortical development. ECM serves as a substrate through which cells migrate and reach their final position. Cingulate gyrus shows different transitory expression pattern of tenascin, neurocan, hyaluronan, glypican and other ECM in comparison to lateral cortical regions, with the most evident difference seen in the marginal zone and the subplate zone. Some of the axon guidance molecules (e.g., Sema5A) show specificities of expression in the medial cortical wall. Since ECM and axon guidance molecules have an important role in neuronal migration, axon elongation, and connectivity formation our goal is to identify the ECM expression profile in the normal fetal brain and concerning the disturbances of ECM expression pattern, its relevance in the pathogenesis of MCD at the vulnerable time points. By the comparative histological-MRI approach (correlating results achieved by immunohistochemical, layer specific transcriptome and in situ MRI method), histological and MRI normotipic parameters will be established as an additional tool in the research and follow-up of pathological features in malformed fetal brains (The study is supported by AF14/17; UniZg0054; Croatian Science Foundation Grant 2015-10-3939 and CoRE – Neuro No.KK.01.1.1.01.0007).

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WDR81 MUTATIONS CAUSE MICROLISSENCEPHALY AND MICROCEPHALY ASSOCIATED TO MITOTIC PROGRESSION DELAY OF NEURAL PROGENITORS

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Microlissencephaly (MLIS) is a rare brain malformation characterized by congenital microcephaly (MIC) and lissencephaly (absent cortical gyrification). MLIS is suspected to result from abnormalities in the proliferation or survival of neural progenitors. Despite the recent identification of six genes involved in MLIS, the pathophysiological basis of this condition remains poorly understood. We performed trio-based whole exome sequencing in 7 subjects from four non-consanguineous families who presented with either MIC or MLIS. This led to the identification of compound heterozygous mutations in WDR81, a gene previously associated with cerebral ataxia, intellectual disability and quadrupedal locomotion (CAMRQ2).

Patient phenotypes ranged from severe (MLIS with or without pontocerebellar hypoplasia) to moderate (MIC with cerebellar hypoplasia). In the patient fibroblast cells, WDR81 mutations were associated with the increased mitotic index and delayed metaphase to anaphase transition. Similarly, in vivo, we showed that knockdown of the WDR81 ortholog (CG6734) in Drosophila led to the increased mitotic index of neural stem cells with delayed mitotic progression. In summary, we highlight the broad phenotypic spectrum of WDR81-related brain malformations, which includes cerebellar atrophy, MIC, and MLIS. Our results demonstrate that WDR81 has a crucial role in mitosis, a role conserved between Drosophila and humans.

PREDICTION OF PERIVENTRICULAR LEUKOMALACIA AND INTRACRANIAL HAEMORRHAGE IN PRETERM INFANTS USING CEREBRAL NEAR-INFRARED SPECTROSCOPY

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In Europe, about 25,000 children are born prematurely every year, their mortality reaches 20%, and among survivors around 25% have some form of the neurodevelopmental disorder, including cerebral palsy. Due to hemodynamic instability caused by transitional cardiopulmonary and respiratory adaptation in the first hours and days of life premature babies are at high risk for brain damage and subsequent neurodevelopmental disorders. Brain damage in premature infants is most commonly seen as peri-intraventricular bleeding (P- / IVH) and periventricular leucomalacia. Their pathogenesis is not fully clarified and is probably multifactorial. According to current research, there is an opinion that hemodynamic instability has an important role in their etiology. Brain injury that occurs after twelve hours of life ("late" P- / IVH) is considered a consequence of hemodynamic instability which implies lack of autoregulation system and/or fluctuation of brain perfusion. Fabres et al. have demonstrated that fluctuations in brain perfusion are the cause of IVH (3rd and 4th grade). To maintain perfusion and vital organ oxygenation, precise therapeutic guidelines have been elaborated, mainly for terminal infants. Interpretation of hemodynamic changes in prematurely born infants is the subject of numerous studies. Due to the proven correlation of hypotension with brain injury, intensive and aggressive interventions such as fluid bolus and/or inotropic drugs are being used in the treatment of hypotension. However, the mean RR value reflects systemic vascular resistance (SVR) and heart output (CO) and has limited value in heart rate (MV) and tissue perfusion monitoring. RR can be preserved in cases of low CO and elevated systemic vascular resistance and vice versa. For these reasons, new methods and ways of monitoring the vital perfusion of vital organs, especially the brain, are being sought. Jobsis first proposed the noninvasive measurement of cerebral oxygenation by near infrared spectroscopy (NIRS) in neonatology, is applied for the first time in 1985. NIRS is a non-invasive method for estimating cerebral hemodynamics that can be continuously used for a longer period and even in babies with very low birth weight. NIRS, using a skin sensor measures regional saturation (rScO2) corresponding to saturation of oxygen-hemoglobin in mixed arterial-capillary-venous tissue vasculature at depths of about two centimeters. NIRS-measured cerebral oxygenation correlates with cerebral blood flow, and rScO2 can be considered a surrogate for brain perfusion. Measurement of cerebral oxygenation was investigated and successfully validated in various diseases and clinical conditions of newborns. The reference values of rScO2 during the first three days of life were published in a recent study involving 999 premies born before the 32nd week of pregnancy. Apart from the estimation of rScO2, NIRS can be used to evaluate fractional

tissue extraction (FTOE), and the autoregulation abnormalities of blood vessels. The results of recent research on the relationship between rScO2 and FTOE with intracranial bleeding (IVH) are contradictory.

This study aims to investigate the relationship between changes in brain tissue saturation measured with NIRS and periventricular leukomalacia and intracranial hemorrhage development in premature newborns born before 32 completed weeks gestational age, detected with magnetic resonance imaging and head ultrasound.

BRAIN MALFORMATION IN A PATIENT WITH DESMOSTEROLOSIS

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Desmosterolosis is an inborn error of metabolism in which desmosterol cannot be degraded due to a deficiency of the enzyme 24-dehydrocholesterol reductase. Desmosterolosis occurs due to mutations in the DHCR24 gene (1p32.3) encoding 3-beta-hydroxysterol delta-24-reductase. This enzyme catalyzes the conversion of desmosterol (the cholesterol precursor) to cholesterol, which is highly involved in embryonic development and morphogenesis. Reduced enzyme activity leads to the accumulation of desmosterol and a lack of cholesterol, disrupting antenatal and postnatal development. Desmosterolosis presents at birth with growth restriction, spasticity with variable degrees of hand contractures, either microcephaly or relative macrocephaly, facial dysmorphism and microretrognathia. Optic atrophy, corpus callosum agenesis and loss of white matter are frequently noted. To date, only nine patients have been described in medical literature. Here I describe a new case, with a novel homozygous missense mutation in the DHCR24 gene.

Our patient is a 6-year-old girl born from consanguineous parents after a full-term pregnancy without perinatal complications and a good start. She presented at our clinic because her mother wondered why her daughter had short stature. Medical history of the patient showed that at the age of 6 months she was found to have microcephaly (-2 SD) and spasticity of the lower extremities (predominantly of the hamstrings). MRI of the brain at the age of 1 year and three months old showed hypoplasia of the corpus callosum, an insufficiently voluminous center semiovale, a wide supratentory ventricular system, irregularly limited ventricular walls and periventricular leukomalacia: this all fits with a diffuse lack of brain matter. At a later age, she developed short stature (length -2.3 SD), a valgus position of the right hip (with trouble walking), a psychomotor developmental delay, obesity and strabismus of the left eye. The patient was initially misdiagnosed as having cerebral palsy due to periventricular leukomalacia obtained due to perinatal asphyxia.

Molecular testing using whole genome sequencing showed a novel homozygous missense mutation in the DHCR24 gene (c.1424A>G, p. (Tyr475Cys)). Biochemical testing in the blood of the patient showed a severe increase in desmosterol: 434 µg/mL (norm 0-7 µg/mL).

Our patient was previously diagnosed with cerebral palsy due to perinatal asphyxia. Because antenatal and perinatal history seemed uneventful, and because of several hallmarks of a problem in brain development (hypoplasia of the corpus callosum, white matter loss, and microcephaly) we were triggered to perform whole exome sequencing in search of a genetic cause for her phenotype. Cholesterol biosynthesis defects often present with brain malformations and other congenital anomalies. The found novel

mutation in the DHCR24 gene in our patient was proven to be pathogenic using biochemical cholesterol analysis (desmosterol was severely increased) and by matching the phenotype of our patient with the nine patients reported in medical literature. We were able to both find an explanation for our patient's neurological phenotype and to answer the question of the mother as to why her daughter had short stature. Unfortunately, there is no curative therapy for desmosterolosis patients, but genetic counseling was now possible.

CORTICAL MALFORMATIONS IN CHILDREN WITH CEREBRAL PALSY CAUSED BY CONGENITAL CYTOMEGALOVIRUS INFECTION

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Congenital cytomegalovirus (cCMV) infection is the most common vertically transmitted infection. Fetal infection occurring in early pregnancy results in severe neurological sequelae, while later infection has less prominent signs.

We present nine patients with cortical malformations and cerebral palsy caused by cCMV infection. Motor functions and accompanying impairments were evaluated according to Surveillance of Cerebral Palsy in Europe (SCPE) recommendations.

According to MRI results we assume that all of our children were infected during the first trimester. Five of our children with lissencephaly/pachygyria had very early onset of infection. The other four with less severe cortical dysplasia in the form of polymicrogyria were probably infected relatively later. Results of cerebellar hypoplasia (3 children) and calcifications (2 children) also confirm an early onset of infection.

Most of the children had bilateral spastic cerebral palsy (7/8), and only one had dyskinetic, subtype dystonic. Gross motor function was severely affected in the majority of children; according to GMFCS, three children had level I-III and 6 level V (wheelchair dependent). All children had some level of intellectual impairment (1 mild, 1 moderate, 7 severe). Speech difficulties were classified using the VIKING speech scale; in 2 children speech was severely affected (level 3) and seven children had no understandable speech (level 4). Epilepsy was found in 8/9 of children. Visual impairment was present in 8/9 children, and 4 of them had a severe visual impairment. Hearing impairment was present in 3 children, and it was classified as severe in 2 of them.

Congenital CMV infection causes multiorgan affection, but the most severe sequelae are those affecting central nervous system. Radiological findings in our study mostly showed lissencephaly/pachygyria, polymicrogyria, calcifications and/or cerebellar hypoplasia that can indicate early and important impact of CMV infection on neurogenesis.

HORIZONTAL GAZE PALSY WITH PROGRESSIVE SCOLIOSIS (HGPPS) AMONG FOUR EGYPTIAN PATIENTS

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Horizontal gaze palsy with progressive scoliosis (HGPPS) is an autosomal recessive disorder characterized by congenital absence of horizontal gaze, progressive scoliosis, and failure of the corticospinal and somatosensory axon tracts to decussate in the medulla. A flattened butterfly-like appearance of medulla with a midline cleft consistent with the absence of tract decussation is a cardinal sign in MRI. It results from homozygous or compounds heterozygous mutations in the axon guidance molecule or receptor-encoding genes, ROBO3 and DCC, respectively. DCC gene related HGPPS was associated with defective corpus callosum development.

Herein, we report five patients from 4 unrelated Egyptian families with HGPPS. They were four females and one male. Molecular testing for either ROBO3 or DCC depended on their neuroimaging differentiation of associated corpus callosum hypo or agenesis. We compare the phenotypic presentation of both genes, and we further investigate the pathway of tracts by diffusion tensor imaging (DTI).

All our five patients presented with HGPPS, and the characteristic neuroimaging findings. Two families were linked to ROBO3 gene, and three were linked to DCC gene associated with corpus callosum agenesis. All recorded mutations were homozygous and novel. (DTI results still in progress). Microcephaly, mental retardation, delayed language development and autistic features were universal in ROBO3 gene while mild mental retardation and autistic features were clear in DCC.

HGPPS can result from biallelic ROBO3 and DCC mutations. Both were equally distributed in our study. Further, we expand the phenotypic and mutational spectrum of this disorder.

CONGENITAL BRAIN MALFORMATIONS AND MRI

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Congenital brain malformations diagnostics has been improved since MRI was introduced as novel technique. For neuropediatric clinicians, it is important to get proper information about the type of anomaly. Congenital brain anomalies are rare and only dedicated pediatric neuroradiologist can distinguish between different types of anomalies as well as recognition of a variety of normal anatomic variants.

MRI is a valuable tool for detecting all brain and spine anomalies. As MRI diagnostics is improving, there are more and more overlapping types of anomalies. Therefore, new classifications are proposed based on neuroimaging. Introducing a "pattern-recognition approach," classification of the type of anomaly is simplified. The role of pediatric neuroradiologist is to define technique as well as the time of neuroimaging. Earlier imaging (fetal MRI) and better spatial resolution, as well as better image details, enable better distinction between different types of anomalies as well as the introduction of new types.

A neuroradiologist is essential in the differential diagnosis, especially in early neuroimaging. Development of brain anomalies has different causes. Th neuroradiologist is able in some cases to distinguish one from another (schizencephaly caused by conatal brain infection (TORCH) for example). For a complete understanding of brain malformations, a multi-disciplinary approach is mandatory, involving experts from neuroembryology, neurogenetics, neurochemistry, pediatric neurology and pediatric neuroradiology.

THE PREVALENCE AND THE ADDING VALUE OF FETAL MRI IMAGING IN CEREBRAL CORTICAL MALFORMATION

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The advances in fetal Magnetic resonance imaging (MRI) with its multiplanar imaging and high contrast resolution, represents the most sensitive imaging modality for the detection and diagnosis of fetal anomalies [1]. We aimed to study the role of MRI in fetal cerebral cortical malformations and compare the results with obstetric ultrasound findings.

Patients and methods: In the two year period between October 2014 to October 2016, eighty fetuses with suspected cerebral malformations in 2,3 and four-dimensional ultrasound underwent both pre and postnatal MRI examination of the brain.

Results: Cerebral cortical disorders diagnosed in 5% of cases, Lissencephaly detected in 50% of them then, Schizencephaly was diagnosed in 25% of them, and Porencephaly detected in 25% of them. Associated anomalies in 75% of them. Maternal age ranged from 25-33-year-old. Diagnosed at gestational age 22- 32 weeks. None of them had the previous history of the affected child, and 25% of them had positive consanguinity. MRI added information in 25% of them. 50% of them died.

In conclusion, ultrasound and MRI are complementary techniques; no one can take place the other except in few cases as in schizencephaly in our study. Good prenatal diagnosis directs the family and the doctor to choose the appropriate way to manage the outcome fetuses with CNS anomalies

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FURTHER DELINEATION OF THE PHENOTYPIC AND MOLECULAR SPECTRUM OF AMPD2 RELATED PONTOCEREBELLAR HYPOPLASIA TYPE 9.

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Ponto cerebellar hypoplasia is a clinically heterogeneous group with 17 different phenotypes and 15 identified causative genes till present. They are rare inherited progressive neurodegenerative disorders of prenatal onset. PCH type 9 is an autosomal recessive characterized by severe microcephaly, severe psychomotor delay, spasticity, intractable seizures. The brain MRI shows hypogenesis of the corpus callosum, cerebellar hypoplasia, ventral pontine degeneration and variable degrees of cortical atrophy. Herein we report 9 Egyptian patients from 8 unrelated families with PCH9. They were five males and four females, aged from 3 months to 2 6/12y and parental consanguinity was in 100% of cases. Patients were identified as candidates for target AMPD2 sequencing based on clinical and neuro-radiological presentation. All had progressive microcephaly, severe global developmental delay, spasticity with intractable generalized and myoclonic seizures and the unique neuroimaging findings as the small cerebellum, hypoplasia of brain stem, hypogenesis of corpus callosum and cortical atrophic changes. Molecular studies Mutational analysis of AMPD2 gene identified six novel mutations and two previously reported in the literature. This study emphasizes the importance of clinical-radiological characterization of PCH9 pointed to target gene sequencing of AMPD2. We further expand the mutational spectrum of this disorder.

Keywords: Ponto cerebellar hypoplasia, AMPD2, Neuroimaging, Neurodegeneration.

TWO SIBLINGS DISPLAY NEURONAL MIGRATION DEFECTS OF DIFFERING SEVERITY WITH BIALLELIC NOVEL MUTATIONS IN RTTN.

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Lissencephaly (LIS) is characterized by smooth cerebral surface and paucity of gyral and sulcal development, associated with deficient neuronal migration. The LIS spectrum includes agyria, pachygyria, and subcortical band heterotopia. The first classification of LIS was developed to distinguish between the first two genetic causes [PAFAH1B1 and DCX]. However, progress in molecular genetics and complex clinical presentations have necessitated a revised classification.

Here we present a family with two affected fetuses with different clinical presentations of disturbed neuronal migration, with the more severely affected fetus having schizencephaly. Both fetuses had a compound heterozygous mutation in RTTN [c.3705C>A and c.4748-19T>A], segregating with the phenotype within the family. RTTN mutations are associated with "microcephaly, short stature, and polymicrogyria with seizures." We aim to broaden the clinical spectrum of cortical anomalies associated with RTTN mutations and emphasize significant intrafamilial clinical variability (the solved antenatal case).

TWO SIBLINGS WITH PROBABLE AUTOSOMAL RECESSIVE LISSENCEPHALY BUT INCOMPATIBLE RADIOLOGICAL PRESENTATION.

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A two-year-old male was referred to the outpatient clinics due to lissencephaly, mental retardation, and seizures. The parents are 1.5-degree cousins, and his four-year-old sister is similarly affected. Both were hypotonic at infancy, with global developmental delay, and seizures with onset at 12 mos of age. Cranial MRI showed cerebral atrophy, lissencephaly with posteroanterior gradient, frontal polymicrogyria, periventricular heterotopia and callosal hypoplasia. Karyotype and LIS1 FISH analyses revealed normal results.

Autosomal recessive lissencephaly subtypes are the first in our differential diagnosis list due to consanguinity of the parents and similarly affected siblings, but the radiological findings indicate towards TUBA1A1 and LIS1 mutations. Clinical presentation of the individuals does not completely correspond to a distinct lissencephaly type. We aim to discuss an algorithm for molecular diagnosis (the unsolved postnatal case).

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VOLUMETRIC ANALYSIS OF DEVELOPING HIPPOCAMPUS IN THE HUMAN FETAL BRAINS WITH AGENESIS OF THE CORPUS CALLOSUM

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One of the most common human brain malformation, agenesis of the corpus callosum (ACC), occurs either in isolated form or associated with other brain anomalies. Since ACC can modify brain morphology, we aimed to determine which consequences this congenital defect has on the prenatal development of the human hippocampus. We analyzed 81 in utero fetal brain MRI scans ranging between 20 gestational weeks (GW) to 38 GW, which were divided into three groups; control group (49 cases), 15 cases with isolated ACC and 17 cases with ACC associated with other brain anomalies. Segmentation of both hippocampi was performed manually and values of intracranial volume (ICV) were obtained from automated segmentations on a 3D reconstructed MRI from a set of 2D axial, coronal and sagittal T2-weighted images. Obtained data were statistically analyzed and presented as a nonlinear regression model for each of three groups and for both hemispheres. Volumes of both hippocampi in all three groups display similar values as well as the same slope of the growth curve in the first phase of the analyzed period. Moreover, after 25th GW there was a significant decrease in hippocampal volume in ACC associated group compared to controls (left: $p = 0.029$; right: $p = 0.020$), and this difference was pronounced even more in the later developmental period. Absolute hippocampal volumes in isolated ACC group start to differ significantly after 28th GW, first for the left hippocampus ($p = 0.007$), and after 29th GW for the right hippocampus ($p = 0.024$) and this difference was more pronounced after 30th GW. In analyzed period, ICVs of control and isolated ACC groups do not significantly differ, while ICVs of ACC associated group showed significantly smaller growth. Our findings indicate that callosal absence notably interferes with the normal process of the hippocampal development during prenatal period in both analyzed groups with ACC, suggesting that this restricted hippocampal growth could affect learning and memory functions in the later life of these infants.

PERINATAL FACTORS ASSOCIATED WITH THE NEUROLOGIC IMPAIRMENT OF BREECH BORN CHILDREN

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About 3 – 4% of all pregnancies reach term with a fetus in breech presentation. Breech presentation is known to be associated with higher perinatal morbidity and mortality than cephalic presentation, perhaps due to the mode of delivery and the higher incidence of congenital anomalies. The routine cesarean section has become the method of choice for breech birth in many hospitals, even though evidence of long-term benefits for infants is still lacking. Two randomized controlled trials and a Cochrane meta-analysis of these trials have not found a planned cesarean section to be associated with substantial benefits for the fetus.

To determine the perinatal risk factors of long-term neurologic impairment for breech born infants.

A case-control study was conducted with 16 neurologically impaired and 43 healthy children, all breech born.

There was no relation between neurologic impairment and maternal pregnancy complications or prenatal steroid administration, the bacteriological content of cervical smear, mode of delivery and fetal heart rate. Cerebral palsy or minimal cerebral dysfunction was associated with neonatal condition at delivery, 5-minute Apgar score, perinatal asphyxia, apnea, convulsion, early neurologic signs and abnormal brain ultrasound findings.

Perinatal asphyxia, apnea, convulsion and early neurologic signs, abnormal brain ultrasound findings and neonatal condition at delivery seem to be risk factors for neurologic impairment of children.

Keywords: neurologic impairment; perinatal asphyxia; breech delivery; perinatal risk factors; preterm birth.

EPILEPTIC ENCEPHALOPATHIES OF UNKNOWN ORIGIN - CASE REPORT OF TWO PATIENTS

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In this case report, two patient with epileptic encephalopathies of unknown origin are shown. Epileptic encephalopathies are severe brain disorders in which epileptic electrical discharges are presumed to contribute to progressive psychomotor dysfunction. In the background often have malformations of cortical development of the brain.They are related to young age, thus creating progressive dysfunction of the developing neurologic system. Depending on the age at onset, the child loses learned skills, or never even acquires them.

First patient, male, now one-year-old, presented at first visit with microcephaly, difficulty feeding, neurodevelopmental delay, impaired vision in observation.He developed myoclonic limb jerks from age two months. EEG polygraphy-generalized epileptiform changes. Brain MRI showed the diffuse simplified gyral pattern in both directions, more pronounced in the area of the insula. Preliminary genetic tests are neat, further testing provided. The second patient, the girl, now 4,5-year-old, born from twin pregnancy (brother is healthy). In the neurological status: tetraparesis, see-saw nystagmus, severe mental retardation. Brain MRI showed pachygyria, Cavum septum pellucide and Cavum Vergae. From age two year has epileptic seizures by type of infantile spasms. The genetic testing is in progress. Various antiepileptic therapy was introduced in both patients, unsuccessfully.

Additional diagnostic treatment will answer the question of etiology of neurodevelopmental delay and medicament resistant epilepsy present in the patients shown in this report, and lead us to a correct diagnosis and therapy

A CASE OF TUBA1A MUTATION PRESENTING WITH CORTICAL MALFORMATION AND PONTO-CEREBELLAR HYPOPLASIA

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Tubulin gene family have an essential role in neuronal migration, axonal guidance, and necessary for the development of the central nervous system. TUBA1A gene is a member of tubulin gene family, coding for alpha I tubulin that constitutes subunit of the microtubule. TUBA1A gene mutation is a relatively rare cause of lissencephaly. The most consistent feature of lissencephaly spectrum due to TUBA1A mutation is severe cerebellar and brainstem abnormalities and agenesis of corpus callosum with congenital microcephaly.

Here, we present a 3/5/12-year old boy who presented with delayed gross mental-motor retardation and congenital microcephaly. He was born at term with normal height and weight. Parents were consanguineous. Cranial magnetic resonance imaging showed dilated ventricular system with irregular margins, pachygyria, sulcation insufficiency, atrophy of cerebellar vermis and hemispheres, pontine atrophy, and hypoplastic corpus callosum. Physical examination at last examination showed generalized hypotonia, hyperextensibility at the elbow, tapering fingers, mild digital clubbing, truncal obesity, and bilateral cryptorchidism. He had some dysmorphic features. He can hold his head, sit unsupported for a short time, and can not speak. He had no eye contact. Whole exome sequencing showed TUBA1A gene mutation.

TUBA1A gene mutation should be considered in the differential diagnosis of patients with cerebellar and brainstem hypoplasia accompanying cortical malformations.

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VLDLR GENE MUTATION IN A 8-YEAR OLD GIRL WITH PONTO-CEREBELLAR HYPOPLASIA

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Very low-density lipoprotein receptor (VLDLR) is part of the reelin (RELN) pathway, which guides neuroblast migration in the cerebral cortex and cerebellum. RELN and VLDLR are important genes for cerebellar development, which play a key role in gait. VLDLR gene mutations cause autosomal recessive, congenital, non-progressive cerebellar ataxia and mental retardation syndrome with or without quadripedal locomotion associated with cerebellar hypoplasia and mild cerebral gyral simplification.

Here, we present an 8-year old girl who presented with delayed gross motor retardation, ataxia, frequent falls and intellectual disability. The prenatal, natal and early postnatal periods of the patient were uneventful. She was born at term with normal birth weight, height and head circumference. She had a history of bilateral inguinal hernia repair at 2 months old and surgery for strabismus at two years old. Cranial magnetic resonance imaging showed severe cerebellar and brainstem atrophy. Physical examination at 8-year old showed generalized hypotonia, hyperextensibility at the elbow, metacarpophalangeal and distal phalangeal joints, sacral dimple and ataxia. She had some dysmorphic features such as the narrow forehead, narrow and long face, abundant eyebrows, prominent nasal root, bulbous nasal tip, long philtrum. She can walk approximately 10 meters independently, and speak 8-10 single words without short sentences. The patient was diagnosed as autosomal recessive pontocerebellar hypoplasia. Whole exome sequencing analysis showed VLDLR gene mutation. VLDLR gene mutation should be considered in the differential diagnosis of the patients with pontocerebellar hypoplasia and non-progressive cerebellar ataxia.

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CLINICAL AND RADIOLOGICAL FINDINGS OF TWO SECOND DEGREE COUSINS WITH NORMAN-ROBERTS SYNDROME

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Many genetic syndromes feature lissencephaly, a cortical malformation characterized by agyria or pachygyria, absence or incomplete development of the cerebral gyri. Autosomal recessive lissencephaly with cerebellar hypoplasia (LCH, Norman Roberts syndrome) is one such entity, with affected individuals having pronounced frontal pachygyria, marked brain stem, and cerebellar hypoplasia. Biallelic mutations in the gene encoding reelin (RELN; 600514) on chromosome 7q22 is responsible for the phenotype. Clinical characteristics include microcephaly, bitemporal hollowing, a low sloping forehead, slightly prominent occiput, hypertelorism, a broad and prominent nasal bridge, and severe postnatal growth deficiency. Neurological features include hypertonia, hyperreflexia, seizures, and severe mental retardation.

We present two-second degree cousins with a definitive diagnosis of LCH with homozygous c.204C>G [p.Tyr68*] in RELN, describe prognosis and clinical/radiological findings. We emphasize ocular findings including severe glaucoma in one affected, a feature that has not been described in PCH patients (solved postnatal case).

INTRAFAMILIAL VARIABILITY AND PRENATAL GENETIC COUNSELING AND IN 6Q27 DELETION SYNDROME

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Deletion of 6q27 is a rare syndrome associated with mental retardation, hypotonia, epilepsy, and multiple malformations. The structural brain malformations observed include agenesis of the corpus callosum, periventricular nodular heterotopia (PNH), polymicrogyria, hydrocephalus and cerebellar malformations.

Here we report a 2-year-old child who has been referred due to the intellectual deficit, epilepsy, and dysmorphisms. An MRI showed periventricular cortical heterotopy. Her mother, who was observed to be mildly affected was pregnant at 16 gestational weeks. Chromosomal array showed that the index and her mother had a deletion of 6q27, spanning about 2,28 Mb of genomic DNA from position 168.619.459 to 170.906.796. Fetal array analysis for the ongoing pregnancy detected the same deletion, and the mother opted for termination of the pregnancy. By reporting the radiological and clinical features family, we draw attention to intrafamilial variability, a feature that can complicate prenatal genetic counseling (the postnatal solved case).

MALFORMATIONS OF CORTICAL DEVELOPMENT IN UNIVERSITY HOSPITAL CENTRE SPLIT: CLINICAL FEATURES AND CAUSES

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Malformations of cortical development (MCD) compose a diverse range of disorders that are common causes of neurodevelopmental delay and epilepsy. This study aimed to investigate the clinical presentation, causes and outcome in 85 children with MCD referred to the Pediatric Clinic of the Clinical Hospital Centre Split from 1998 to 2018. MCD was diagnosed based on MRI.

Outcomes were the worst for 27 children with early diffuse MCD and nine children with bilateral polymicrogyria (PMG). All of them had epilepsy, 11 epileptic encephalopathies, poor developmental and neurological outcome and 8 of them died. Less severe disabilities showed 12 children with unilateral PMG and schizencephaly: 4 of them developed generalized epilepsy, three mild unilateral spastic cerebral palsy GMFCS I-II, and all of them were intellectually normal. The better outcome showed five children with heterotopias and three children with focal cortical dysplasia: 5 of them had epilepsy with no other disabilities, but one of them had intractable seizures. We established an etiological diagnosis in 27 children.

We concur with other authors that MCD illustrate the ability of the human brain to compensate for seemingly severe alterations in its normal developmental architecture. The input of the clinician remains necessary to link clinical, imaging and genetic data, to define precisely clinical-imaging entities, and to improve patient treatment and disease management.

CONGENITAL MALFORMATIONS AND NEURORADIOLOGY

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The continuous development of the various MRI techniques brought a different perspective in analysis and understanding of congenital brain anomalies and their classification. The number and complexity of recognized congenital brain anomalies have been increasing over last few decades, mainly as the result of improvement based on MRI neuroimaging. Multiple "new classifications" have been proposed based upon neuroimaging findings (Dandy-Walker specter for example). In one exam may exist more than one malformation. The role of pediatric neuroradiologist is to recognize all types and patterns of brain anomalies and to determine a necessity of neurosurgical intervention or conservative treatment. Using novel MRI techniques such as diffusion tensor imaging (DTI) and tractography allow better understanding the inner neuroarchitecture of the normally and abnormally developing brain. Therefore, neurosurgical treatment can be more precise and can preserve normal part of brain or spine tissue as well as its function.

The role of neuroradiologist is to provide: proper exam interpretation, to categorize better various brain malformations that may look similar with conventional imaging, but may have different etiologies, to get additional information by analyzing and correlating various new neuroimaging techniques, to detect the complex functional/anatomic relation between various, distant functional centers within a malformed brain.

All experts from neuroembryology, neurogenetics, neurochemistry, pediatric neurology and pediatric neuroradiology should be included in brain malformation diagnostics. A multi-disciplinary approach is the foundation for good and complete understanding of brain malformations.

GENETIC BASIS OF BRAIN MALFORMATIONS

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Malformations of cortical development (MCD) represent a major cause of developmental disabilities, severe epilepsy, and reproductive disadvantages. Genes that have been associated with MCD are mainly involved in cell proliferation and specification, neuronal migration, and late cortical organization. Lissencephaly-pachygyria-severe band heterotopia are diffuse neuronal migration disorders causing severe global neurological impairment. Abnormalities of the LIS1, DCX, ARX, RELN, VLDLR, ACTB, ACTG1, TUBG1, KIF5C, KIF2A, and CDK5 genes have been associated with these malformations. More recent studies have also established a relationship between Lissencephaly, with or without associated microcephaly, corpus callosum dysgenesis as well as cerebellar hypoplasia, and at times, a morphological pattern consistent with polymicrogyria with mutations of severe genes (TUBA1A, TUBA8, TUBB, TUBB2B, TUBB3 and DYNC1H1), regulating the synthesis and function of microtubules and centrosome key components, and hence defined as tubulopathies. MCD is only affecting subsets of neurons, such as mild subcortical band heterotopia and periventricular heterotopia, have been associated with abnormalities of the DCX, FLN1A, and ARFGF2 genes and cause neurology Polymicrogyria results from the abnormal late cortical organization and is inconstantly associated with abnormal neuronal migration. Localized polymicrogyria has been associated with anatomy-specific deficits, including disorders of language and higher cognition. Polymicrogyria is genetically heterogeneous, and only in a small minority of patients, a definite genetic cause have been identified. Megalencephalic with normal cortex or polymicrogyria by MR imaging, hemimegaloencephaly, and focal cortical dysplasia can all result from mutations in genes of the PI3K-AKT-mTOR pathway. Postzygotic mutations have been described for most MCD and can be limited to the dysplastic tissue in the less diffuse forms. Ical and cognitive impairment that varies from severe to mild deficits.

Keywords: Lissencephaly, Malformation, Cortical development

CHARACTERISTICS OF CHILDREN WITH CEREBRAL PALSY AND BRAIN MALDEVELOPMENTS IN REGISTER OF CEREBRAL PALSY OF CROATIA

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This study aims to evaluate the characteristics of children with cerebral palsy (CP) and brain maldevelopments.

This study was based on the data of children with a diagnosis of CP, from the SCPE National Register C28 - Register of cerebral palsy of Croatia, born from 01/01/2007 to 31/12/2008.

Results: In this period 153 children, who were later diagnosed with CP, were born in the area of the register. Out of them, 106 (69.28%) had available brain MRI findings. They were divided, as proposed by SCPE, into 5 categories: brain maldevelopments (17/106; 16.04%), predominant white matter injury (56/106; 52.83%), predominant gray matter injury (16/106; 15.09%), miscellaneous changes (13/106; 12.26%) and normal findings (4/106; 3.77%).

In the group of children with brain maldevelopments, five children had lissencephaly/pachygyria, four polymicrogyria, one hemimegaloencephaly, one schizencephaly, three dysgeneses of the corpus callosum, one focal cortical dysplasia, one subependymal heterotopia and one complex malformation. Out of this 17 children, 15 had spastic CP (2 unilateral and 13 bilateral) and two dyskinetic CP (both dystonic subtype). According to Gross Motor Function Classification System, two children had level I, 5 level II, 2 level III, 2 level IV and 6 level V. Intellectual impairment was classified into three categories: 12 children had IQ <50, 3 IQ 50-70 and only 2 IQ≥70. Speech difficulties were classified using the VIKING speech scale: level I, II and III had two children in each category and level IV 10 children (for one child VIKING level was unknown). Epilepsy was found in 11/17 of children, and at the time of registration, all of them had active epilepsy. Visual impairment was present in 9/17 children, and 3 of them had a severe visual impairment. Hearing impairment was present in 1 child, and it was classified as severe. In conclusion, children with CP and brain maldevelopments have multiple severe accompanying impairments.

CHANGES IN MR SIGNAL INTENSITY AND MICROSTRUCTURE OF TRANSIENT FETAL ZONES AS INDICATORS OF GROWTH AND DEVELOPMENT OF AXONAL PATHWAYS IN THE HUMAN BRAIN

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Development of fiber pathways in the human brain is a complex process which can be disrupted by many different factors. Transient fetal zones which play an important role in axonal growth, navigation, elongation, and recognition of postsynaptic elements. Two key zones for axonal growth are subplate and intermediate zone (fetal white matter); but each of five segments of white matter, described by Von Monakow, has its relevance in the normal and pathologic development of the brain. Different classes of fiber pathways have distinct periods of intensive growth and development, which leads to increase of vulnerability to noxious factors in these periods. Development of MRI techniques enabled us to visualize brain development in-vivo, and it became possible to diagnose various disorders of the fiber pathway growth in fetuses and prematurely born children. Fractional anisotropy (FA) and other MRI-DTI scalars are used to represent microstructural changes in different pathologies of white matter, both in adult brain and developmental neurobiology. Although many studies investigated the development of the fiber pathways, the spatial relationship between growing fiber pathway and subplate, and MR characteristics of normal and abnormal growth of fiber pathways in subplate zone are still unknown. Knowing white matter pathways growth dynamics through white matter segments during normal brain development, changes of MR signal intensity and microstructural MRI-DTI parameters will reflect more directed fibers in the segment I regarding subplate, but later will be more structurally organized comparing to periventricular crossroads in segment II. All of this proportions are expected to be changed in different neurodevelopmental lesions. The goal of this study is a quantification of microstructural changes of white matter segments during normal and disturbed processes of brain development, for a better understanding of the basis of neurodevelopmental disorders and the clearer correlation between MRI-exam and clinical parameters. A cohort of 50 prematurely born children are MRI examined at preterm and term equivalent age, third MRI will be performed in their second year of life. All of these MRI scans will be analyzed by volumetric-analysis and MRI DTI programmes. Using MRI volumetric and microstructural analysis, clinical parameters and the neurodevelopmental outcome is expected to make a correlation between MRI and clinical outcome more tangible, especially in mild, and merely to notice, MRI developmental changes of the brain development. (Supported by CSF-IP-09-2014-4517 and CSF-DOK-10-2015; co-financed by the European Union through the European Regional Development Fund, Operational Programme Competitiveness, and Cohesion, grant agreement No.KK.01.1.1.01.0007, CoRE – Neuro).

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DELINEATION OF THE PHENOTYPIC AND MUTATIONAL SPECTRUM OF ASPM-RELATED PRIMARY MICROCEPHALY IN EGYPT

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Autosomal recessive primary microcephaly (MCPH) is a proliferative disorder of brain development that leads to a small brain size but architecturally normal. Although microcephaly is genetically heterogeneous and more than 18 causative genes have been identified to date, but *ASPM* gene is still the most prevalent. Thirty-seven patients from 30 unrelated families with a clinical diagnosis of MCPH were enrolled in this study. Screening of *ASPM* gene mutations was performed by linkage analysis followed by direct sequencing. Thirteen protein truncating mutations of the *ASPM* were identified in 15 families (50%), eight of which were novel mutations. The mutations detected were eight nonsense, four frameshifts, and one splice site. Two of these mutations (p.Arg1327*, p.Arg3181*) were recurrent and shared similar haplotypes suggesting founder effect. *ASPM*-positive patients had an occipital-frontal circumference greater than -5 SD, mild to severe intellectual disability and variable degrees of simplified gyral pattern and frontal lobe hypoplasia. In addition, hypoplasia of corpus callosum, mild cerebellar-vermis hypoplasia, and relatively small pons ware found in 85.7%, 47.6% and 61.9%, respectively. Moreover, one patient had porencephaly and another showed small midline cyst. Epilepsy was documented in two 9.5% of patients. Non-neurologic abnormalities consisted of growth retardation at the time of examination (4 patients), and oculo-cutaneous albinism (1 patient). This study is the first of its kind from Egypt, to identify the phenotype associated with *ASPM* mutations. Further, our results expand the mutation spectrum of *ASPM*.

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