13th International Conference of Baltic Child Neurology Association

EESTI ARST
Eesti Arst 2015;(Supplement1):1–88


EMGS
Eesti Meditsiinigeneetika Selts
Estonian Society of Medical Genetics


EESTI LASTENEUROLOOGIDE SELTS


Eesti
Epilepsialiit


PTC
THERAPEUTICS
Translating Science. Transforming Lives.


TEVA


Shire


genzyme
A SANOFI COMPANY


sobi
SWEDISH ORPHAN BIOVITRUM


Tartu University Hospital


ORPHAN EUROPE
RECORDATI GROUP


European Union
European Social Fund
Investing in your future


Tartu
city of good thoughts


MEDA


Laste fond
Tartu Ülikooli Kliinikum


Embassy of the
United States of America


Manpower


NOVARTIS
PHARMACEUTICALS


BIOCODEX


NUTRICIA
Advanced Medical Nutrition


IPSEN
Innovation for patient care


SANOFI


CADWELL


SA TALLINNA LASTEHAIGLA


LUX Express


LIVIKO
anno 1898


Kalev


emt


Elion

13th International Conference of Baltic Child Neurology Association

May 13-16, 2015
Tartu

Dear colleagues and friends,

On behalf of the Scientific and Organizing Committee, we would like to welcome you at the 13th Conference of the Baltic Child Neurology Association (BCNA) that takes place in Tartu, Estonia, May 13-16, 2015, in the Dorpat Conference Centre.

The conference will celebrate the 25th anniversary of the BCNA, which was founded in Tartu in 1990. The first BCNA conference was also held in Tartu in 1991.

This year the conference is held in collaboration with the Baltic Metabolic Group and in conjunction with their annual Metabolic Meeting dedicated to Neurometabolics.

The conference will provide top-level education and state of the art information, particularly targeted at pediatric neurologists, pediatricians and geneticists.

A combination of an excellent scientific and innovating programme with a number of social events planned for the conference will offer you many possibilities to strengthen scientific collaboration, renew friendships, find new friends, and enjoy the old university town of Tartu.

Tartu – a city of good thoughts - with its population of 100,000, is the second largest city in Estonia and the centre of Southern Estonia. Tartu is home to one of the oldest universities in Northeast Europe, which was founded in 1632 by Swedish King Gustavus II Adolphus.

With the time-honoured university in its heart, the museum-rich Hanseatic city of Tartu lies on the banks of the river Emajõgi, which flows for 10 kilometres within the city limits adding colour to its inviting surroundings.

Welcome to Tartu at the 13th Conference of BCNA!

On behalf of the Organizing Committee

Tiina Talvik
Conference President

Inga Talvik
Secretary General

Eve Õiglane-Shlik
Secretary

SCIENTIFIC COMMITTEE

Tiina Talvik (Estonia)
Inga Talvik (Estonia)
Eve Õiglane-Shlik (Estonia)
Anneli Kolk (Estonia)
Nerija Vaičiene-Magistris (Lithuania)
Milda Endziniene (Lithuania)
Jurgis Strautmanis (Latvia)

LOCAL ORGANIZING COMMITTEE

Tiina Talvik
Inga Talvik
Klari Noormets
Eve Õiglane-Shlik
Katrin Maiste
Stella Lilles
Anneli Kolk
Ulvi Vaher
Aita Napa
Valentin Sander
Kaidi Lunge
Marika Kirss
Evelyn Evert
Airi Tenno
Heli Grünberg

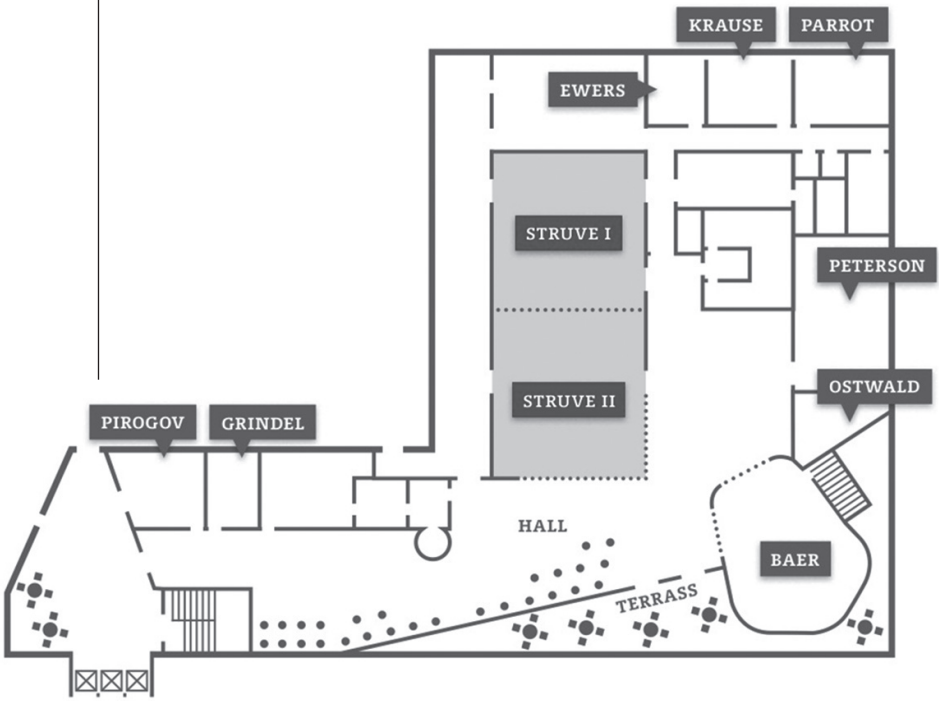
INVITED SPEAKERS

Randell Alexander
Walter van Emde Boas
J Helen Cross
Eija Gaily
Hans Goebel
Katrin Gross-Paju
Pilvi Ilves
Daniela Karall
Adam Kirton
Leo A. J. Kluijtmans
Alfried Kohlschütter
Lieven Lagae
Holger Lerche
Rima Nabbout
Kelly St. Pier
Mart Saarma
Ola Didrik Saugstad
Sabine Scholl-Bürgi
Werner Stenzel
Katrin Õunap
Sarah Weckhuysen

CONFERENCE VENUE

Dorpat Conference Centre, located on the 4th floor of the adjoining Tasku Centre, is the largest and most contemporary conference and event centre in Southern Estonia. The centre offers ten multifunctional rooms of various sizes, among which every client is sure to find one that best suits their needs. To pay homage to the University of Tartu, the rooms are named after the city's most famous scientists and professors. All of the rooms have the necessary technical equipment, such as data projectors, screens, flipcharts and a sound system, which are included in the room price. The entire centre has free wireless Internet access and guests can use a public computer in the lobby.

The conference complex includes a spacious lobby used for catering events; also, it is ideal for organizing exhibitions and fairs. In addition, movable walls enable you to change the floor plan, so that the Struve and Baer rooms can be connected to the lobby.



How was the Baltic Child Neurology Association (BCNA) born?

The BCNA was founded on 7.09.1990 in Tartu on the initiative of three chief child neurologists of the Baltic States: Milda Rimsiene (1933-2009, Lithuania), Nikolai Gatt (Latvia) and Tiina Talvik (Estonia). Probably, Nikolai Gatt was the first who came forward with the idea to create the Baltic Association. The aim of the new Association was to unite Baltic child neurologists, to have better possibilities for learning and training and to create patient- and family-oriented medical care for children, as well as to gain strength from unity, to make more friends and, last but not least, to have fun and to enjoy being together.

Among the first invited speakers was Prof. Helena Pihko (from Helsinki) who told us about mitochondrial disorders. Another very important guest speaker was the mother of a boy with CP, Anne Mellgren (Sweden). She was also President of the International Cerebral Palsy Society, and the topic of her talk was parents' expectations when they raise a child born with disability.

The First International Conference of the BCNA was held in Tartu on September 18–20, 1991. We, people from the Baltic States, still remember our feelings in August 1991 when Soviet tanks entered the Baltic States and many people from abroad cancelled their conference registration. Nevertheless, many world famous specialists still came to Tartu: Pirkko Santavuori (Finland), Jean Aicardi (France), Martin Bax (UK), John Stephenson (UK), Alfried Kohlschütter (Germany), Karin Nelson (USA, Bethesda), Marja-Liisa Grandström (Finland), Matti Iivanainen (Finland), as well as Ljubov Trofimovna Zurba and Boris Viktorovits Lebedev from Moscow. Since this first meeting, many of them have remained our dear friends and constant supporters for years and even up to the present day.

At the beginning of the 1990s the possibilities to attend conferences abroad were very limited. We were able to travel only with the support of our friends from other countries (Finland, Sweden, Norway, German, UK). So, organizing local training courses and workshops was the most realistic way of educating ourselves. The BCNA was registered in May 1991 by the Estonian Ministry of Health (Dr. Andres Ellamaa).

Over all these years the presidents or vice presidents of the BCNA as well as the conference presidents have been Prof. Nerija Vaiciene (Lithuania), Prof Milda Endziniene (Lithuania), Prof Egils Vitols (Latvia), and Prof. Tiina Talvik (Estonia); the secretary generals have been Prof. Milda

Endziniene (Lithuania); Aleksandrs Kovaldins, Sarma Lindenberga, Baiba Norite, Jurgis Strautmanis, and Guntis Rozentals (Latvia); Prof Irja Lutsar, Anu Sööt (PhD), Anneli Kolk (PhD), Associate Prof. Inga Talvik (Estonia).

Now, at the 25th anniversary of the BCNA foundation, the history repeats itself to a certain extent. When at the time of the first conference we had a political crisis, then in 2009 we had a worldwide economic crisis and today there is war in Europe.

We are very pleased to have met and known prominent professors of child neurology during our conferences: Y. Suzuki, K. Swaimann, P. Santavouri, M.-L. Granström, W. Logan, L. Shield, S. Wallace, L. Dubowitz, V. Dubowitz, B. Neville, H. Cross, A. Kohlschütter; Walter van Emde Boas, J. Stephenson, H. Pihko, I. Tein, M. Bax, K. Nelson, V. Lebedev, L. Zurba, M. Iivanainen, S. B. Naidu, O. D. Saugstad, U. Stephani, R. Nabbout, Y. Fukuyama, M. Segawa, and many others. We are grateful to all of them.

We wish all our young colleagues to have the motivation and wish to keep the BCNA in good shape with interesting conferences and a friendly family of the BCNA.

On behalf of the Organizing Committee of the 13th Conference
Tiina Talvik
Conference President

Schedule

Dorpat Conference Centre, Tartu, Estonia

MAY 13, 2015

BALTIC METABOLIC MEETING 2015

Chairs: Prof. Katrin Õunap/Kairit Joost, PhD

11.00-12.00 Registration and welcome coffee

12.00-12.45 Next generation metabolomics. Leo Kluijtmans (The Netherlands)

12.45-13.15 Where are we after one year newborn screening pilot study? Katrin Õunap (Estonia)

13.15-13.45 From clinical symptoms to diagnosis of metabolic diseases. I. Micule, Z. Krumina (Latvia)

13.45-14.05 *DARS2* gene defect: two case reports with different clinical presentations. Eve Õiglane-Shlik (Estonia)

14.05-14.25 Complete sequencing of mitochondrial genome allows to identify two patients with Leigh and Leigh-like syndrome. Dita Pelnena (Latvia)

14.30-15.30 Lunch

15.30-15.50 A 5-year-old boy with progressive epileptic encephalopathy and severe developmental delay caused by novel compound heterozygous mutations in the *CACNA1A* gene. Karit Reinson (Estonia)

15.50-16.10 Laboratory findings in mucolipidosis type II (I-cell disease). Jurgita Songailiene (Lithuania)

16.10-16.30 Screening for congenital disorders of N-glycosylation in Estonia. Mari-Anne Vals (Estonia)

16.30-16.45 Case report: adult onset Pompe disease. Kairit Joost (Estonia)

16.45-17.00 Early diagnosis of mevalonate kinase deficiency and efficacy of anakinra. Birute Burnyte (Lithuania)

17.00-17.30 Baltic Metabolic Group Meeting

16.00-19.00 TEACHING COURSE I: UPDATE IN MYOPATHOLOGY

Chairs: Prof. Hans Goebel/Prof. Werner Stenzel

16.00-17.00 Muscular dystrophies and congenital myopathies. Hans Goebel (Germany)

17.00-18.00 Inflammatory diseases of the skeletal muscle. Werner Stenzel (Germany)

18.00-18.10 Medical management of Duchenne muscular dystrophy in Minsk, Belarus. Nastassia Biahanskaya (Belarus)
18.10-18.20 Variations in LGMD genes *CAV3* and *FKRP*. Janis Stavusis (Latvia)
18.20-18.30 Case presentation. Klari Noormets (Estonia)
18.30-18.40 Case presentation. Eve Õiglane-Shlik (Estonia)
18.40-19.00 Overview of the current situation and plans for the future: Estonia, Latvia, Lithuania.
19.30-22.00 Welcome party, Dorpat Conference Hall

MAY 14, 2015

8.00-8.45 TEACHING COURSE II: CHILDHOOD ISCHAEMIC STROKE
Chairs: Prof. Tiina Talvik/Prof. Adam Kirton/Ass. Prof. Katrin Gross-Paju
Childhood ischemic stroke: Challenges and advances. Adam Kirton (Canada)

9.00-9.20 Opening Ceremony

9.20-12.25 NEUROMETABOLICS
Chairs: Prof. Alfried Kohlschütter/Prof. Katrin Õunap
9.15-10.00 Experimental and palliative treatment of CLN2 disease (late-infantile neuronal ceroid lipofuscinosis). Alfried Kohlschütter (Germany)
10.00-10.45 The expanding spectrum of mitochondrial disorders - usefulness of mitoNET network. Daniela Karall (Austria)
10.45-11.30 Ketogenic diets in inborn disorders of metabolism. Sabine Scholl-Burgi (Austria)
11.30-11.45 Reversible infantile respiratory chain deficiency in Estonia. Kairit Joost (Estonia)
11.45-12.00 Late Onset Glucose transporter 1 (GLUT1) deficiency syndrome. Sandra Melnik (Lithuania)
12.00-12.15 Outcome of GLUT1 deficiency syndrome in a 2-year-old Estonian girl. Stella Lilles (Estonia)
12.15-12.25 Discussion
12.25-13.15 Lunch/Posters
Chairs: Prof. Lieven Lagae/Prof. Nerija Vaičiene-Magistris
- Interleukin-2 and interleukin-2-receptor in children with epilepsy. Ruta Praninskiene (Lithuania)
- Wolf-Hirschhorn syndrome: A case report. Asta Judickiene (Lithuania)
- Rare causes of poor weight gain: CNS tumor in a 3-year-old boy. Simona Jaksyte (Lithuania)
- Osmotic demyelination syndrome in a 11-year-old otherwise healthy boy. Diana Akeliene (Lithuania)

- Early case of tuberous sclerosis complex. Karolina Liaušiene (Lithuania)
- Do methylenetetrahydrofolate reductase (*MTHFR*) polymorphisms raise homocysteine levels in children with migraine? May B vitamins help? Anna-Liisa Lorenz (Estonia)
- An interstitial deletion of chromosome 7q35q36.1 in a 3-year-old boy with clinical features of Weaver syndrome. Laura Roht (Estonia)

13.15-15.15 NEUROGENETICS

Chairs: Prof. Lieven Lagae/Prof. Rima Nabbout

13.15-13.45 The mTOR system and neurology. Milda Endziniene (Lithuania)
13.45-14.15 Tuberous Sclerosis Complex: an update on neurological aspects. Rima Nabbout (France)
14.15-14.25 Tuberous Sclerosis Complex: Situation in Estonia. Valentin Sander (Estonia)
14.25-14.35 Latvian experience: The efficiency of everolimus in tuberous sclerosis patients with subependymal giant cell astrocytoma (SEGA). Diana Volčeka (Latvia)
14.35-14.45 Everolimus in young patients with tuberous sclerosis complex. Lingvita Gumbelevičiene (Lithuania)
14.45-14.55 Levodopa responsive dystonia in children. Jolita Urbonaite (Lithuania)
14.55-15.05 The first deep brain stimulation in Lithuania for generalized dystonia in a teenager. Nerija Vaičiene-Magistris (Lithuania)
15.05-15.15 Discussion
15.15-15.30 Coffee/tea

15.30-19.00 EPILEPSY

Chairs: Prof. J Helen Cross/Prof. Milda Endziniene

15.30-16.00 Classification of the epilepsies: Old and new with relevance to clinical practice & epidemiological studies. J Helen Cross (UK)
16.00-16.30 Consciousness and epileptic seizures: where are we? Walter van Emde Boas (The Netherlands)
16.30-17.00 Treatment of patients with Dravet syndrome. Rima Nabbout (France)
17.00-17.30 The risks and benefits of valproate. Eija Gaily (Finland)
17.30-17.45 Cannabinoids for the treatment of epilepsy. J Helen Cross (UK)
17.45-18.00 Non-pharmacological treatment of epilepsy: Estonian experience. Ulvi Vaher (Estonia)
18.00-18.15 Atypical idiopathic focal epilepsies with centrotemporal spikes: from clinical features to fMRI. Ruta Samaitiene (Lithuania)
18.15-18.45 The genetic revolution in childhood epilepsy: also evolution to better care? Lieven Lagae (Belgium)
18.45-19.00 Discussion

MAY 15, 2015

8.00-8.45 TEACHING COURSE III: PERINATAL STROKE
Chairs: Prof. Adam Kirton/Anneli, Kolk PhD
Perinatal stroke: Mechanisms of injury and outcomes. Adam Kirton (Canada)

9.00-11.30 EPILEPSY GENETICS
Chairs: Prof. Holger Lerche/Ass. Prof. Inga Talvik

9.00-9.30 Mechanisms and therapeutic consequences of genetic epilepsies. Holger Lerche (Germany)
9.30-10.00 Genetics of epilepsy: what recent discoveries have taught us. Sarah Weckhuysen (Belgium)
10.00-10.30 Algorithms for epilepsy genetic testing. Birute Tumiene (Lithuania)
10.30-10.45 The use of chromosomal microarray in children with epilepsy – Estonian experience. Klari Noormets (Estonia)
10.45-11.00 Targeted next generation sequencing as a diagnostic tool in 170 patients with epileptic encephalopathies. Rikke S Møller (Denmark)
11.00-11.15 Epileptic encephalopathies – lessons learned. Inga Talvik (Estonia)
11.15-11.30 Four cases of CDKL5-related epileptic encephalopathy in Estonia: 1 female and 3 male patients. Stella Lilles (Estonia)
11.30–11.45 Coffee/tea

11.45-13.45 STROKE IN CHILDREN
Chairs: Prof. Adam Kirton/Ass. Prof. Pilvi Ilves

11.45-12.20 Neuroimaging in pediatric stroke: Diagnosis, prognosis, and plastic recovery. Adam Kirton (Canada)
12.20-12.35 Epilepsy after perinatal stroke. Rael Laugesaar (Estonia)
12.35-12.50 A retrospective study: cerebral ischemic stroke in children and young people at the Children's Clinical University Hospital (Riga, Latvia). Mikus Jakovickis (Latvia)
12.50-13.05 Risk factors, clinical and radiological findings in presumed perinatal stroke. Pilvi Ilves (Estonia)
13.05-13.20 Neurodevelopmental outcome after neonatal and presumed perinatal stroke at preschool to early school age. Silva Lõo (Estonia)
13.20-13.45 Discussion
13.45-14.45 Lunch/posters
Chairs: Prof. Alfried Kohlschütter/Prof. Walter van Emde Boas

- Ophthalmoplegic migraine in childhood: case report. Jurate Laurynaitiene (Lithuania)

- Incidence of childhood epilepsy in Estonia. Kadi Veri (Estonia)
- Antiepileptic drugs used in the treatment of European neonates contain potentially harmful excipients - analysis of the ESNEE point prevalence study. Anu Bärenson (Estonia)
- Findings of neuroimaging in children with developmental disabilities. Jurgita Grikiniene (Lithuania)
- Tammistu Family Centre – a competence centre for families of children with rare disorders. Tiina Stelmach (Estonia)
- Tuberous sclerosis complex and epilepsy: ten years of experience. Dovile Jonuškaite (Lithuania)

14.45-16.15 TEACHING COURSE IV: CHILD ABUSE
Chairs: Prof. Randell Alexander/Ass. Prof. Inga Talvik
- Adverse childhood experiences and the brain
- Abusive head trauma 2015
- Physical abuse

14.45-16.30 CLINICAL NEUROPSYCHOLOGY AND NEUROREHABILITATION IN CHILDREN
Chair: Academician Mart Saarma/Anneli Kolk, PhD

14.45-15.15 Neurotrophic factors in the development and plasticity of the nervous system. Mart Saarma (Finland)
15.15-15.25 New trends in pediatric neurorehabilitation. Anneli Kolk (Estonia)
15.25-15.35 The impact of epilepsy on social competence and cognitive function in 7-12- year-old children. Triin Raud (Estonia)
15.35-15.45 Generalized effect of cognitive neurorehabilitation in children with epilepsy based on parental feedback. Agne Põlder (Estonia)
15.45-15.55 Personalized approach and importance of individual differences in pediatric neurorehabilitation. Marianne Saard (Estonia)
15.55-16.10 Advances in pediatric stroke rehabilitation: Non-invasive brain stimulation. Adam Kirton (Canada)
16.10-16.30 Discussion
16.30-16.45 Coffee/tea

16.45-18.30 NEONATAL NEUROLOGY
Chairs: Prof. O. D. Saugstad/Eve Õiglane–Shlik, PhD

16.45-17.15 HIE – impact of asphyxia and reoxygenation. Ola Didrik Saugstad (Norway)
17.15-17.30 Outcome for 2-year-olds born at very low gestational age in Estonia: are there any improvements? Heili Varendi (Estonia)
17.30-17.45 Gender differences in developmental outcomes of Estonian preterm children at the age of two and five years and the relationships between the outcomes. Mairi Männamaa (Estonia)

17.45-17.55 The outcome of newborns with very low Apgar score at Tartu University Hospital in 2004-2014. Anne Antson (Estonia)
17.55-18.05 Prevalence and mortality among children with spina bifida in Lithuania: an assessment in a European context from 1990 to 2010. Indre Bakaniene (Lithuania)
18.05-18.30 Discussions
20.00 Reception of the City Major Mr. Urmas Klaas and Gala Dinner, White Hall of the University of Tartu Museum

MAY 16, 2015

8.00-8.45 TEACHING COURSE V: DRUG RESISTANT EPILEPSY
Chairs: Prof. van Emde Boas/Prof. J Helen Cross

9.00-10.45 NEUROIMMUNOLOGY
Chairs: Prof. Nerija Vaičiene-Magistris/Ass. Prof. Katrin Gross-Paju
9.00-9.30 Contemporary and future management of patients with multiple sclerosis. Katrin Gross-Paju (Estonia)
9.30-9.55 Paediatric multiple sclerosis: when we should doubt about diagnosis. Nerija Vaičiene-Magistris (Lithuania)
9.55-10.05 Challenges in diagnosis of autoimmune encephalitis in children. Inga Talvik (Estonia)
10.05-10.15 Clinical case presentation of LGl 1 antibody positive encephalitis. Karin Kannel (Estonia)
10.15-10.45 Discussions

10.45-12.45 VARIA
Chairs: Prof. Randell Alexander/Valentin Sander
11.00-11.45 Abusive head trauma. Randell Alexander (USA)
11.45-11.55 Novel homozygous mutation in KPTN gene causing a familial intellectual disability-macrocephaly syndrome. Sander Pajusalu (Estonia)
11.55-12.05 Familial porencephaly – clinical and neuroimaging manifestations in persons with *COL4A1* gene mutation. Kristi Simenson (Estonia)
12.05-12.15 Joubert syndrome – an example of ciliopathy. A family case presentation. Riina Žordania (Estonia)
12.15-12.30 Methods of intraoperative neurophysiology. Kaidi Lunge (Estonia)
12.30-12.45 Discussion

12.45-13.15 Closing ceremony
Farewell lunch

DARS2 gene defect: two case reports with different clinical presentations

Eve Õiglane-Shlik[1,2], Kairit Joost[3], Tiia Reimand[2,3,4], Sander Pajusalu[2], Tiiu Tomberg[5], Katrin Õunap[2] – [1]Children's Clinic, Tartu University Hospital, Tartu, Estonia; [2]Department of Pediatrics, University of Tartu, Tartu, Estonia; [3]Department of Genetics, United Laboratories, Tartu University Hospital, Tartu, Estonia; [4]Institute of Biomedicine and Translational Medicine, Department of Biomedicine, University of Tartu, Tartu, Estonia; [5]Radiology Clinic, Tartu University Hospital, Tartu, Estonia

Mutations in the *DARS2* gene encoding mitochondrial aspartyl-tRNA synthetase cause leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL). LBSL is a rare autosomal recessive disease that was initially described as a relatively mild disorder characterized by juvenile onset of slowly progressive ataxia, spasticity and dorsal column dysfunction. Recent observations have revealed that the phenotypic spectrum in LBSL is much wider than originally presumed, ranging from adult-onset oligosymptomatic cases to patients with infantile onset and rapid neurological deterioration and early demise.

Here we describe two Estonian patients with genetically confirmed LBSL, but with different phenotypes. The first patient underwent a regular brain ultrasound at the age of 6 months, which revealed diffuse white matter signal deterioration. Subsequent brain MRI confirmed findings consistent with LBSL. The patient is now 5 years old and symptom free. The second patient was hospitalized due to sudden right side hemiparesis and gait clumsiness. He was markedly ataxic and developed signs of bulbar paralysis, requiring insertion of gastrostomy to ensure his feeding. His brain MRI revealed diffuse leukoencepalopathy with concomitant spinal cord involvement. His condition improved considerably after intravenous corticosteroid therapy. Analysis of the *DARS2* gene revealed that both patients were compound heterozygotes who shared one common *DARS2* mutation, a c.228-21_-20delTTinsC, and different mutations in the other allele, c.455G>T and c.492+2T>C respectively. Although the genotype c.228-20delTTinsC/ c.492+2T>C (patient 2) presents clinically in childhood and patients with the genotype c.228-21_-20delTTinsC/ c.455G>T (patient 1) present later, they both have relatively benign phenotypes characterized by mildly progressive neurological deterioration (van Berge *et al* 2014).

CONCLUSION. *DARS2* mutations should be considered in patients with leukoencephalopathy and concomitant spinal cord involvement. Changes characteristic of LBSL are detectable by MRI long (?) before the appearance of clinical symptoms.

Complete sequencing of mitochondrial genome allows to identify two patients with Leigh and Leigh-like syndrome

Dita Pelnena[1], Baiba Lace[1], Inna Inaskina[1], Janis Stavusis[1], Zita Krumina[2], Liana Pliss[1], Eriks Jankevics[1] – [1]Latvian Biomedical Research and Study Centre, Riga, Latvia; [2]Children's Clinical University Hospital, Medical Genetics Clinic, Riga, Latvia

INTRODUCTION. Mitochondrial diseases are severe multisystem organ disorders which can be caused by mutations in mtDNA as well as in nuclear DNA. Combination of clinical observations, biochemical and molecular analysis is required to establish precise diagnosis.

MATERIALS. The mtDNA of 58 samples was analyzed by direct sequencing from 2012. Seven of them were from healthy individuals and 51 were from patients with suspected mitochondrial disease.

METHODS.The mtDNA was amplified as 12 overlapping fragments. We designed 96 oligonucleotides for the uniform sequencing reaction set up with a single melting temperature of 56ºC. Sequencing with these primers allowed 4–6-fold coverage of the mtDNA genome.

RESULTS. Mutations in the genes *mt–ATP6* and *mt–ND5* were identified in two patient samples and hence Leigh syndrome and Leigh–like syndrome were confirmed. The first patient is a girl aged three with seizures, and psychomotor and emotional retardation, absence of speech, microcephaly, generalized hypotonia, spasticity in legs and dystonia in the upper extremities. Heteroplasmic mutation mt.9185T>C was identified in the gene *mt–ATP6* causing amino acid change p.Leu220Pro.

The second patient is a boy aged five. He has had seizures since the age of six months, psychomotor retardation, generalized hypotonia and speech development delay. MRI showed abnormalities in the brain stem and basal ganglia and severe loss of periventricular white matter. Heteroplasmic mutation mt.13513G>A was found in the gene *mt–ND5* resulting in amino acid change p.Asp393Asn.

CONCLUSIONS. We have confirmed Leigh syndrome and Leigh–like syndrome in two patients with symptoms of mitochondrial disease by sequencing mtDNA. During the studies several unpublished mutations of unclear clinical significance have been identified (mt.5573A>G, mt.13760C>T).

A 5-year-old boy with progressive epileptic encephalopathy and severe developmental delay caused by novel compound heterozygous mutations in the *CACNA1A* gene

Karit Reinson[1,2], Eve Õiglane-Shlik[2,3], Tiia Reimand[1,2,4], Rita Teek[1,2], Sander Pajusalu[1,4], Anne Õunapuu[5], Ülle Murumets[1], Katrin Õunap[1,2] – [1]Department of Genetics, United Laboratories, Tartu University Hospital, Tartu, Estonia; [2]Department of Paediatrics, University of Tartu, Tartu, Estonia; [3]Children's Clinic, Tartu University Hospital, Tartu, Estonia; [4]Institute of Biomedicine and Translational Medicine, Department of Biomedicine, University of Tartu, Tartu, Estonia; [5]Neurology Clinic, Tartu University Hospital, Tartu, Estonia

Familial hemiplegic migraine, episodic ataxia, and spinocerebellar ataxia type 6 are autosomal-dominant neurological disorders associated with heterozygous mutations in the *CACNA1A* gene. Some patients may exhibit overlapping phenotypes, which combine various signs characteristic of these three conditions. The *CACNA1A* gene encodes the pore-forming α1 subunit of the neuronal voltage-gated calcium channel $Ca_v2.1$ mediating the action-potential-evoked neurotransmitter release in the central nervous system.

In the index patient, absence of eye contact was noted at the age of 2 months. Severe muscular hypotonia, arrested development and frequent epileptic seizures were observed later. At first MRI revealed white matter hypomyelination and thin *corpus callosum*, thereafter diffuse cerebellar and cerebral atrophy developed. At the age of 5 years he has profound developmental delay, muscular atrophy with rigidity, dysmorphic features and treatment resistant epilepsy. He is blind. Muscle biopsy showed lipid deposits in muscle fibers. His elder sister died at the age of 5 years due to similar epileptic encephalopathy. Two elder sisters and both parents have mild intellectual disability. The mother has also ataxia and cerebellar atrophy.

Exome sequencing identified novel compound heterozygous mutations in the *CACNA1A* gene – a missense mutation c.4315T>A predicted pathogenic and a frameshift deletion c.472_478delGCCTTCC. Sanger sequencing confirmed both mutations in the index patient and in his deceased sister. The mother and one elder sister carry c.4315T>A, and the father and the second elder sister carry c.472_478delGCCTTCC mutation.

This is the first description of a patient with a compound heterozygous mutation in the *CACNA1A* gene, which causes severe epileptic encephalopathy.

This study was supported by the Estonian Research Council grant PUT355.

Screening for congenital disorders of N-glycosylation in Estonia

Mari-Anne Vals[1,2], Dirk Lefeber[3], Katrin Õunap[1,2] – [1]Department of Genetics, United Laboratories, Tartu University Hospital, Tartu, Estonia; [2]Department of Pediatrics, University of Tartu, Tartu, Estonia; [3]Department of Neurology, Translational Metabolic Laboratory, Radboud University Medical Center, Nijmegen, The Netherlands

INTRODUCTION. Congenital disorders of glycosylation (CDG) are a growing group of inheritable metabolic diseases. It comprises four different categories, and protein N-glycosylation defects are the most common group of CDG. Its clinical spectrum and severity is wide. If N-glycosylation disorder is suspected, first transferrin isoelectric focusing (TIEF) should be done, as 75% of patients show abnormal type I or type II pattern. In 2008, the first patient with PMM2-CDG was diagnosed in Estonia. In 2012, TIEF was introduced in Estonia to diagnose CDG among our patients. If an abnormal pattern in TIEF is found, additional investigations are indicated to confirm the diagnosis.

METHODS. Serum TIEF was used to screen patients with suspicion of metabolic disease (June, 2012 – March, 2015). The results of analyses were provided by geneticists, paediatricians, neurologists and psychiatrists.

RESULTS. Serum TIEF was performed to 1004 patients. So far, we have detected seven patients (0.7%), whose TIEF pattern is suggestive of CDG. Three of them had type I pattern and four had type II pattern. With additional investigations, two patients with suggestive type II pattern were considered to have normal transferrin glycosylation, one patient has a combined defect of N- and O-glycosylation and the results for four patients are still inconclusive.

CONCLUSIONS. Although the clinical picture of CDG is unspecific, all patients with unexplained neurological symptoms, cerebellar atrophy, coagulopathy and/or growth failure should be screened for CDG. Introduction of TIEF in Estonia has helped to diagnose or to exclude N-glycosylation defects among our patients. Nevertheless, it should be kept in mind that among 25% of CDG patients, TIEF is found to be normal. Depending on the type of CDG suspected, alternative diagnostic methods should be considered.

Early diagnosis of mevalonate kinase deficiency and efficacy of anakinra

Birute Burnyte[1,2], Skaiste Peciuliene[2], Rymanta Gudaitiene[2], Skirmante Rusoniene[3], Jurgita Songailiene[1], Arunas Liubsys[2], Nijole Drazdiene[2] – [1]Department of Human and Medical Genetics, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [2]Neonatology Centre of Vilnius University, Vilnius, Lithuania; [3]Pediatrics Centre of Vilnius University, Vilnius, Lithuania

BACKGROUND. Mevalonate kinase deficiency (MKD) is an autosomal recessive inflammatory disorder caused by a mutation in the mevalonate kinase (*MVK*) gene. Severe enzyme deficiency results in mevalonic aciduria (MA) and milder deficiency in Hyperimmunoglobulinemia D syndrome (HIDS).

CASE REPORT. The patient was born at 33 weeks by cesarean section because of hydrops fetalis with a weight of 2676 g. Apgar score 8/8. Immediately after birth hypotonia, hepatosplenomegaly, metabolic acidosis, severe anemia and intense acute phase reaction were observed. From the 2nd week of life failure to thrive, lethargy and short (1-2 days) recurrent febrile episodes with bloody diarrhoea started. Metabolic screening that was performed at 2 weeks revealed an increased urinary excretion of mevalonic acid lactone, supporting the MKD diagnosis. Genetic testing showed a homozygous mutation within the *MVK* gene. Before the MKD diagnosis, treatment with broad-spectrum antibiotics and antifungal agents showed poor responses. After MKD diagnosis, corticosteroids and antioxidant medication (coenzyme Q10) was administered, as well as continuous partial parenteral feeding and occasional red blood cell transfusions.

ANAKINRA THERAPY. Because of the persistence of febrile episodes and systemic inflammatory reaction, off-label treatment with the anti-IL-1 agent anakinra was begun at 2 months of age continuously (1,5 mg/kg/day). After 3 days from starting anakinra, systemic inflammatory reaction markers returned to normal and did not increase later on. After 1 month of treatment cessation of febrile episodes, weight gain and marked improvement of psychomotor development was noticed.

CONCLUSIONS. In our patient with MKD continuous treatment induced complete remission. However, long term follow-up is needed for quality of life management and possible side effects.

TEACHING COURSE I: UPDATE IN MYOPATHOLOGY

Muscular dystrophies and congenital myopathies

Hans H. Goebel – Department of Neuropathology, Charité University Medicine, Berlin, Germany

Muscular dystrophies (MD) are a very heterogeneous group of progressive hereditary neuromuscular disorders.

Myopathology - the topic of this workshop – can significantly contribute to some but not all of the MD. Apart from a basic pattern of histopathology, immunohistochemistry identifies individual forms of MD, such as dystrophinopathies, sarcoglycanopathies, dysferlinopathy, and certain congenital muscular dystrophies (CMD) when respective proteins are reduced or completely deficient. Western blots may confirm or further clarify the nosological diagnosis, but subsequent molecular analysis is essential for the final diagnosis of an individual MD. Based on recent molecular findings, the number of genetically different MD has recently been considerably increased.

Congenital myopathies (CM) are marked by structural abnormalities in skeletal muscle to which immunohistochemistry can contribute very little information. Nevertheless, identification of the genes recognized in individual CM has considerably complicated the once rather clear spectrum of CM. For instance, the morphological condition "Nemaline Myopathy" has no been assigned to mutations in nine different genes.

The relevant myopathology of these MD and CM will be presented in numerous examples.

Inflammatory diseases of the skeletal muscle

Werner Stenzel – Department of Neuropathology, Charité - Universitätsmedizin, Berlin, Germany, Berlin, Germany

Traditionally, inflammatory myopathies were diagnosed on the basis of a certain clinical syndrome, laboratory results, electromyography and the myopathological evaluation of a muscle biopsy.

Recently, several additional parameters have been taken into consideration; among these are myoimaging and modern serological auto-antibody testing methods. The current classification of inflammatory myopathies (IIMs) comprises polymyositis (PM), dermatomyositis (DM), immune-mediated necrotizing myopathy (IMNM) and sporadic inclusion body myositis (sIBM) and, finally, non-specific myositis (NSM).

However, this classification has been subject to intense critique at various levels. First, the entity of polymyositis has been questioned, since many of these patients developed either sIBM, are grouped among the NSM/overlap myositis group. In addition, it is unclear whether sIBM is really an inflammatory myopathy although its inflammatory component at biopsy is unquestionable. However, any of the anti-inflammatory regimens employed to date have failed to treat sIBM conclusively. Second, dermatomyositis encompasses a multitude of very different subgroups with different clinical, therapeutical and prognostic implications. It has been shown only recently that certain subgroups can be defined by different myositis specific auto-antibodies such as TIF1gamma, MI-2 NXP2 or MDA-5, with TIF1gamma being associated with systemic malignancy while MI-2-positive patients show classical dermatomyositis with good response to treatment.

Third, a subgroup, which was recently added to the IIMs is the necrotizing myopathies which basically comprise two large groups, SRP- and HMGCR-associated myopathies. Both of them can be easily diagnosed by antibody testing and they certainly present with a very characteristic morphological pattern as well.

Lastly, a number of rare inflammatory myopathies have to be mentioned, among them granulomatous myositis, eosinophilic myositis and the macrophagic myositis.

These entities will all be presented, and their clinical, serological and morphological characteristics will be discussed in detail.

Medical management of Duchenne muscular dystrophy (DMD) in Minsk, Belarus

Nastassia Biahanskaya – Minsk, Belarus

AIM. To evaluate the quality of medical management of children with DMD in Minsk.

METHODS. Detailed interviews of families and affected children, clinical examination and study of medical records.

RESULTS. Most patients receive their clinical diagnosis of DMD at the age of 5–6 years after repeated medical examinations by pediatric neurologists and rehabilitation treatment at a specialized center. All patients undergo genetic testing, which in many cases is negative. Some parents repeat testing abroad and sometimes they get information about the disease. Electroneuromyography is always done but muscular biopsy is not provided. Common medications are multivitamins, coenzyme Q-10, vitamin E, levocarnitine, meldonium etc. Only a few receive prednisolone owing to prescriptions provided by doctors abroad, but in these cases steroid therapy is not well controlled. About half of the patients have ankle-feet orthoses but sometimes they use them for twenty-four hours and get deteriorated. Some patients do regular stretches and physical exercises (including breathing exercises), although most parents dare not aware of their importance. Hydrotherapy is not prescribed. Nobody who is asymptomatic receives cardioprotective therapy even if there occur the first changes on ultrasonography or in the electrocardiogram. Annual influenza vaccination is not prescribed nor is prescribed varicella or 23-pneumo vaccination. Only a few patients have stenders. Families do not receive adequate psychological support. In a rehabilitation center patients often pass a course of massage, training on a treadmill, electrophoresis of medicine, foot baths, acupuncture and receive recommendations for a healthy diet.

CONCLUSION. National medical management of DMD needs significant changes to improve the quality of life of patients and to increase their life expectancy. It is necessary to create a registry of patients with genetically confirmed DMD in order to have an opportunity to participate in international trials. To ensure a multidisciplinary approach, it is necessary to increase the level of knowledge of different specialists through compiling and distributing pamphlets on European recommendations for the medical management of DMD, as well as through inviting experienced lecturers from abroad.

Variations in LGMD genes *CAV3* and *FKRP*

Janis Stavusis[1], I. Inashkina[1], E. Jankevics[1], I. Radovica[1], I. Micule[1], J. Strautmanis[1], M.S. Naudina[1], A. Utkus[2,3], B. Burnyte[2,3], B. Lace[1] – [1]Latvian Biomedical Research and Study Centre, Riga, Latvia; [2]Department of Human and Medical Genetics, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [3]Centre for Medical Genetics, Vilnius University Hospital Santariškių Klinikos, Vilnius, Lithuania

Limb-girdle muscular dystrophies (LGMD) are a heterogeneous group of untreatable, degenerative muscle diseases. The goal of this study was to characterize variations in *CAV3* and *FKRP* genes in patients with LGMD.

The coding region and exon/intron boundaries of the *CAV3* gene were sequenced in 81 neuromuscular disorder patients, a sample group from the Genome Data Base, consisting of 97 individuals with cardiomyopathies, as well as a random selection of 100 persons. The coding region and exon/intron boundaries of the *FKRP* gene were sequenced in 65 neuromuscular disorder patient samples.

Standard Sanger sequencing was used for detection of sequence variations, immunochemical staining with CAV3 antibodies was performed by a standard protocol to verify findings in one patient, who underwent muscle biopsy due to the rapid progression of the disease.

Three novel sequence variations (c.183C>G, p.S61R; c.220C>A, p.R74S; c.220C>T, p.R74C) were identified in the *CAV3* gene and evidence was found for one being associated with hyper-creatine-kinase-emia. Three previously reported mutations (c.183C>G, pSer61Arg; c.216C>G, p.Cys72Trp; c.233C>T, p.T78M) were found in families with limb girdle muscular dystrophy. No mutations were identified in the cohort of patients with cardiomyopathies.

In the *FKRP* gene the reported disease causing mutation c.826C>A, p.Leu276Ile was found in three LGMD patient samples, one of which was in a homozygous state. The other two were compound heterozygous cases with two novel mutations, c.delCTC204_206 and c.404_405insT, respectively.

The *CAV3* gene encodes muscle-specific protein with a dominant negative type of missense mutations in it, causing various phenotypes. Our study confirmed *CAV3* gene variation involvement in neuromuscular disorders, but found no evidence in the group of patients with cardiomyopathies.

Findings in the *FKRP* gene make it one of the first-choice genes when considering LGMD diagnostics among the Latvian population.

TEACHING COURSE II: CHILDHOOD ISCHAEMIC STROKE

Childhood ischemic stroke: Challenges and advances

Adam Kirton – Calgary Pediatric Stroke Program, Alberta Children's Hospital Research Institute, Departments of Pediatrics and Clinical Neurosciences, University of Calgary, Calgary, Canada

The care of children with ischemic stroke is often challenging for the pediatric neurologist.

Arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT) are medical emergencies where prompt diagnosis and early management can improve outcomes.

Pressing issues in AIS include improving delays in diagnosis, the role of acute thrombolytic and endovascular interventions, understanding pathophysiology of leading causes such as arteriopathies, secondary stroke prevention strategies, and rehabilitation to improve long-term function. Similar priorities in CSVT include improved recognition of risk factors, optimizing diagnostic imaging, and the role of anticoagulation therapy. Recent advances will be presented within a practical clinical framework aimed to enhance the ability of attendant child neurologists to care for children with ischemic stroke.

NEUROMETABOLICS

Experimental and palliative treatment of CLN2 disease (late-infantile neuronal ceroid lipofuscinosis)

Alfried Kohlschütter – Department of Pediatrics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Neuronal ceroid lipofuscinoses (NCL) are a large group of genetic metabolic degenerative brain diseases that lead to dementia and other sever functional losses in childhood. Among them is (according to the present classification) late-infantile CLN2 disease, which is caused by the deficiency of a lysosomal enzyme, tripeptidyl peptidase 1 (TPP1) in the brain. The disease usually starts around the third year of life with developmental standstill and/or severe epilepsy, followed by gradual loss of all cognitive as well as motor abilities and death between 10 and 15 years of age. I will (I) illustrate an efficient approach to early diagnosis, which may, apart from its usefulness for family counselling, gain additional importance in view of the recent development of enzyme replacement therapy in several animal models of the disease, including a dog with important similarities to young CLN2 patients. I will (II) describe our first experience with repeated infusions of a preparation of TPP1 directly into a lateral brain ventricle of a cohort of 12 affected children, using a reservoir implanted in the skull that is accessible by skin puncture, and will (III) comment on various aspects of palliative treatment in CLN2 patients, some of which are typical of many severe neurological conditions while others require an understanding of the specific disease.

Reversible infantile respiratory chain deficiency in Estonia

Kairit Joost[1], Haide Põder[2], Andres Piirsoo[3], Kristina Kall[4], Kaidi Lunge[2], Riina Žordania[1] – [1]Department of Genetics, United Laboratories, Tartu University Hospital, Tartu, Estonia; [2]Tallinn Children's Hospital, Tallinn, Estonia; [3]Institute of Biomedicine and Translational Medicine, University of Tartu, Estonia; [4]Central Laboratory of the Health Board, Tallinn, Estonia

Mitochondrial disorders are usually severe and progressive conditions which often have a fatal outcome. However, recently several rare forms of the diseases have emerged with significantly favourable prognosis showing spontaneous recovery if infants survive the first months of life. Reversible infantile respiratory chain deficiency (RIRCD) caused by mutation m.14674T>C in the mitochondrial $tRNA^{Glu}$ gene is one of these disorders characterized with hypotonia in infancy, followed by recovery occurring around 1 year of age.

AIM. To describe 2 patients with RIRCD.

Patient 1 presented during the first days of life with transient hypoglycemia and tachypnea. At the age of 1 month, following the vaccination, clinical deterioration occurred presenting with severe muscular hypotonia and respiratory distress. Electromyographic investigation (EMG) showed myopathic findings, whereas brain MRI showed no pathology. Her muscular biopsy performed at the age of 2 months revealed a pathological ultrastructure of mitochondria, ragged red fibres (RRF) and lowered COX activity.

Patient 2 was hospitalized at the age of 2 months due to deterioration during acute respiratory infection. Clinically, muscular hypotonia was observed. Her biochemical workup was suggestive of mitochondrial disorder, but brain MRI and ENMG revealed no pathology. Still, patomorphological muscle investigations revealed pathological mitochondria and some glygcogen storage.

RESULTS. Biochemical workup from the muscle reavealed deficient activity of respiratory chain (RC) complexes I and IV confined to muscle in both patients. Molecular genetic studies revealed homoplasmic mutation m.14674T>C $mtRNA^{Glu}$.

The clinical course, treatment and genealogical data of both patients are discussed.

CONCLUSION. Reversible mitochondrial phenotypes (including RIDCD) have favourable outcome and should therefore be considered in the early stages of differential diagnosis in infants presenting with mitochondrial dysfunction and myopathy.

Late Onset Glucose transporter 1 (GLUT1) deficiency syndrome

Sandra Melnik[1], Ruta Praninskiene[1,2] – [1]Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [2]Department of Pediatric Neurology, Children's Hospital, Affiliate of Vilnius University Hospital Santariskiu Clinic, Vilnius, Lithuania

Key words: epilepsy, movement disorder, encephalopathy, hypoglycorrhachia, ketogenic diet

AIM. Glucose transporter type 1 deficiency syndrome (GLUT1DS) is a treatable condition, resulting from impaired glucose transport into the brain due to a mutation in SLC2A1 gene. The classical presentation is with infantile-onset epilepsy and severe developmental delay. Non-classical phenotypes involve early-onset absence epilepsy and movement disorders, provoked by infections, exercise and fasting. The hallmark is hypoglycorrhachia in the presence of normoglycaemia with a CSF/blood glucose ratio of <0.4. However, in patients with the late-onset phenotype, CSF/blood glucose ratio can be <0.59.

METHOD. This case report describes a patient with late onset GLUT1-DS.

RESULTS. A 3-year 6-month-old girl presented with paroxysms with full consciousness: rapid jerking of one or both lower extremities, falling down or developing rolling gait. Further she developed learning difficulties and attention deficit hyperactivity disorder, but there was no family history of movement disorders or epilepsy. At the age of 5 she experienced the first generalized tonic-clonic seizure after tonsillitis. Later she developed absence type of seizures. Brain MRI was normal, there were no pathological findings in blood and urine analyses. The interictal EEG showed normal background activity with 3Hz generalized spike–slow wave complexes. Over the years, the patient`s condition aggravated, paroxysms intensified after upper respiratory tract infections. She failed treatment with Valproic Acid, Lamotrigine, Topiramate, Levetiracetam, Clonazepam, Nitrazepam. Movement disorders continued with Carbamazepine but absences responded to Ethosuximide. Lumbar puncture revealed low CSF glucose concentration of 2.5 mmol/l, normal blood glucose concentration of 5.1mmol/l. The CSF/blood glucose ratio was 0.49. The patient was diagnosed with GLUT1DS and treatment with a ketogenic diet was initiated.

CONCLUSION. This case demonstrates that GLUT1-DS should be investigated in individuals with refractory absence seizures and fluctuating movement disorders.

Outcome of GLUT1 deficiency syndrome in a 2-year-old Estonian girl

Stella Lilles[1], Ulvi Vaher[1], Kati Toom[2], Katrin Õunap[3,4], Tiina Talvik[1,3], Inga Talvik[1,3] – [1]Children's Clinic, Tartu University Hospital, Tartu, Estonia; [2]Neurology Clinic, Tartu University Hospital, Tartu, Estonia; [3]Department of Pediatrics, University of Tartu, Tartu, Estonia; [4]Department of Genetics, United Laboratories, Tartu University Hospital, Tartu, Estonia

INTRODUCTION. Glucose transporter-1 (GLUT1) deficiency syndrome is treatable encephalopathy caused by heterozygous mutations of the SLC2A1 gene and results in inadequate glucose delivery to the brain, which leads to hypoglycorrhachia. The clinical spectrum is wide, but it is classically characterized by treatment-resistant epilepsy, developmental delay and complex movement disorders.

CASE REPORT. The patient was born at term from a first non-consanguineous normal pregnancy and uneventful delivery. She presented with delayed psychomotor development, central hypotonia, trunk and limb ataxia and quite modest epilepsy. She had first seizures at the age of 10mo and at 1y 4mo she had had 3 generalized tonic seizures and 3 focal seizures. All interictal electroencephalograms were normal and she was treated with levetiracetam. Magnetic resonance imaging at 10mo and 1y 5mo indicated delayed myelination. Full metabolic work-up was negative, except for elevated plasma alanine. Because of suspected mitochondrial disorder, muscle biopsy was performed at 1y 5mo, which was without pathological changes. At the age of 2y 1mo cerebrospinal fluid (CSF) analysis showed low CSF glucose (2.0 mmol/l) and a decreased CSF-to-blood glucose ratio (0.358) in the absence of hypoglycemia. Sequence analysis of SLC2A1 revealed a heterozygous mutation (c.968_972del p.V323Afs*56) and GLUT1 deficiency syndrome was diagnosed at the age of 2y 1mo. Treatment with a ketogenic diet was started immediately with favourable response in seizures, psychomotor development and ataxia. The patient is seizure free and antiepileptic treatment has been stopped. She has positive dynamics in psychomotor development. She started to walk without aid at 3y, and at 3y 3mo her psychological development corresponds to that of a 2y 6mo old child.

CONCLUSION. This is the first case of GLUT1 deficiency syndrome diagnosed in Estonia. Recognizing GLUT1 deficiency syndrome is important as it can effectively be treated by means of a ketogenic diet.

The study was supported by the EuroEPINOMICS grant SARLA11091E.

Interleukin-2 and interleukin 2-receptor in children with epilepsy

Rūta Praninskienė[1], Irena Dumalakienė[2], Mykolas Mauricas[2], Aurelija Jučaitė[3] – [1]Department of Child Neurology, Vilnius University Children's Hospital, Vinius, Lithuania; [2]Department of Immunology, State Research Institute Center for Innovative Medicine, Vilnius, Lithuania; [3]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Elevated levels of cytokines have been reported in patients with the prolonged febrile seizures, suggesting their contribution to neuronal injury in relation to epilepsy. Elevated serum levels of interleukin-2 (IL-2) have been reported in West syndrome and in relation to carbamazepine therapy.[1, 2] It has been observed that IL-2 is following a circadian pattern of melatonin.[3] We have recently reported a group of children with epilepsy with high nocturnal melatonin concentrations.[4] In the present study we further examined the levels of IL-2 and its receptor sIL-2R in 25 children with epilepsy and in 13 control children, mean age 13.2 (3) yrs and 10.5 (3.8) years, respectively. The salivary melatonin and urinary metabolite 6-sulphatoxymelatonin levels were also examined. ELISA assays were used. All children were afebrile, without concomitant infections. Relationship between epilepsy characteristics, peak melatonin and IL-2, sIL-2R levels was analysed.

RESULTS. Cytokine IL-2 levels correlated significantly with body mass index (general linear model, $F = 9.6$, $p = 0.04$). IL-2 and sIL-2R levels were numerically higher in children with epilepsy (n.s.). There were no correlates between IL2-sIL-2R levels and peak melatonin concentrations or clinical seizure characteristics.

COMMENTS. The study suggests that levels of IL2, a lymphocyte marker of immune response, may not be altered in children with epilepsy.

REFERENCES

1. Liu ZS, Wang QW, Wang FL, Yang LZ. Serum cytokine levels are altered in patients with West syndrome. Brain Dev 2001;23:548–51.
2. Pacifici R, Paris L, Di Carlo S, Bacosi A, Pichini S, Zuccaro P. Cytokine production in blood mononuclear cells from epileptic patients. Epilepsia 1995;3:384–7.
3. Lissoni P, Rovelli F, Brivio F, Brivio O, Fumagalli L. Circadian secretions of IL-2, IL-12, IL-6 and IL-10 in relation to the light/dark rhythm of the pineal hormone melatonin in healthy humans. Nat Immun 1998;16:1–5.
4. Praninskiene R, Dumalakiene I, Kemezys R, Mauricas M, Jucaite A. Melatonin secretion in children with epilepsy. Epilepsy Behav 2012;25:315–22.

Wolf-Hirschhorn syndrome: A case report

Asta Judickiene, Ruta Praninskiene – Department of Neurology of Children's Hospital, Affiliate of Vilnius University Hospital Santariskiu Clinics, Vilnius, Lithuania

BACKGROUND. Wolf-Hirschhorn syndrome (WHS) is characterised by mental retardation, epilepsy, growth delay and craniofacial dysgenesis. The incidence is estimated at 1 in 50.000 births. Wolf-Hirschhorn syndrome is more common in females as compared to males, with a male-to-female ratio of 1:2.

WHS occurs due to deletion of the short arm of chromosome 4 (band 4p16.3).

CASE REPORT. A 3-year-old girl (S.S.) from the third pregnancy first presented with prenatal onset growth deficiency followed by postnatal growth retardation, hypotonia, microcephaly, a distinct "Greek warrior helmet" face with characteristic broad-beaked nose, prominent glabella, hypertelorism, micrognathia and frontal bossing. In line with moderate delay in psychomotor development, hearing defect was documented.

Febrile seizures manifested at the age of 1 year 6 months, afebrile epileptic focal seizures with generalization started at the age of 2 years 6 months.

WHS (deletion of the short arm of chromosome 4, band 4p16.3) was detected by FISH (fluorescence in situ hybridization) technique using a WHSC1 and CEP4 probes.

CONCLUSION. Chromosomal abnormalities are an important cause of neurodevelopmental delay, seizures and congenital anomalies.

In a child with clinically obvious psychomotor retardation and epileptic seizures associated with dysmorphic features and congenital anomalies, cytogenetic studies or FISH analysis may help establish a specific diagnosis which can predict clinical outcome.

Rare causes of poor weight gain: CNS tumor in a 3-year-old boy

Simona Jaksyte, Jurgita Grikiniene, Edita Janoniene, Violeta Gulbiniene – Children's Hospital Affiliate of Vilnius University Hospital Santariskiu Clinics, Department of Neurology, Vilnius, Lithuania

INTRODUCTION. Primary tumours in the central nervous system (CNS) are one of the most common malignancies in childhood. Apart from the signs of elevated intracranial pressure, less likely nonspecific symptoms as visual system abnormalities, weight loss, macrocephaly and growth failure may also suggest presence of an intracranial tumour, especially in young children. Pilocytic astrocytomas are slow growing, generally well demarcated tumors. Pilocytic astrocytomas occur predominantly in children and young adults.

CASE. A 3-year old boy was admitted due to poor weight gain, poor apetite, suspected metabolic disease. Food allergy was observed in infancy and poor weight gain from the age of 1 year 4 months was obvious. Even social problems in the family were highly suspected. On the clinical examination evident muscle and hypodermis hypotrophy, strabismus convergens and some other focal neurological symptoms were noted. Body weight was 10 kg (2 kg under 3rd percentile), height/weight under 3rd percentile, head circumference 85-97 percentiles. All routine laboratory tests were normal but lactate concentration was slightly increased and alanine concentration was below normal level. Differential diagnosis between hereditary metabolic disorder and genetic disorder was considered. Fundoscopic examination revealed a smaller and brighter right optic nerve disc. Brain MRI scan showed tumour in sella turcica area, 73x47x63 mm, and occlusive hydrocephalus. Dysregulation of hypophysis-hypothalamus axis hormones was detected. Surgical operation was performed. The final hystologic diagnosis was pilocytic astrocytoma grade I.

CONCLUSIONS. Vision assessment and appropriate plotting of growth and head size as well as the more widely recognised symptoms of elevated intracranial pressure and motor dysfunction are important in the diagnosis of brain tumours.

Osmotic demyelination syndrome in a 11-year-old otherwise healthy boy

Diana Akelienė[1], Gitana Bykova[2], Jūratė Laurynaitienė[1], MildaEndzinienė[1] – [1]Department of Neurology, Lithuanian University of Health Sciences, Kaunas, Lithuania; [2]Department of Child Intensive Care Unit, Lithuanian University of Health Sciences, Kaunas, Lithuania

INTRODUCTION. Osmotic demyelination syndrome (ODS) is a rare, often lethal disorder involving central pontine and/or extrapontine demyelination process. Only a few cases of ODS have been reported from a pediatric population and most of them concern children with chronic diseases.

CASE REPORT. A 11- year-old previously healthy boy was hospitalized because of permanent vomiting for 5 days and severe hypovolemia. He was diagnosed with food intoxication and underwent international protocol-based fluid replacement therapy with isotonic and hipotonic NaCl infusion. On the 7th day of the disease and on the 2th day of hospitalization the patient developed moderate hyponatremia, which continued for more than 48 hours despite correction. On the 6th day of hospitalization, after more intensive correction of hyponatremia with isotonic NaCl infusion (correction rate 11 mmol/L within 4 hours), rapid elevation of plasma sodium level was observed. Despite subsequent reduction in the sodium level and correction rate up to acceptable (8 mmol/L/24 hours), 3 days later the patient developed neurological symptoms: horizontal and vertical nystagmus, double vision, dysarthria, dysphagia, right tongue deviation, rigidity and stiffnes of the right leg, mild dyscoordination, ataxia, right-side dysdiadochokinesis, inconstant Kernig's sign. MRI showed hyperintense symmetric areas in the lower part of *medulla oblongata*. After a careful differential diagnosis of other demyelination diseases the diagnosis of ODS was confirmed.

CONCLUSION. Electrolyte dysbalance should be corrected with particular precaution in all patients with chronic hyponatremia, even mild, in order to prevent the development of harmful ODS. For pediatric patients, we provide slower correction of hyponatremia, to prevent ODS, compared with that recommended in the new guidelines (2014) on the diagnosis, classification, and treatment of true hypotonic hyponatremia.

Early case of tuberous sclerosis complex

Karolina Liaušienė, Milda Endzinienė, Virginija Ašmonienė, Jūratė Laurynaitienė, Aušrelė Kudrevičienė – Lithuanian University of Health Sciences, Kaunas, Lithuania

INTRODUCTION. Tuberous sclerosis complex (TSC) is an inherited neurocutaneous disorder that manifests with benign hamartomas of the brain, kidney, heart, lung, liver, eyes, and skin. Tumour-suppresor genes (TSC1 and TSC2) are involved in most cases, a small number of patients have deletions that inactivate both the TSC2 gene and the polycystic kidney disease 1 gene (PKD1) that is located nearby (the TSC2/PKD1 contiguous gene syndrome). Affected patients have clinical features of both TSC and polycystic kidney disease, and typically present with early-onset renal cystic disease.

CASE REPORT. We present a case of a woman with TSC, with a negative family history of TSC. Ventriculomegaly was observed during prenatal ultrasound investigation. After birth, multiple cysts in both kidneys (maximum 6.6 x 11.3 mm), ventriculomegaly, white matter heterotopia, subependymal nodules, hypoplasia of temporal lobes, multiple heart rhabdomyomas, hamartoma in the left eye, and one hypopigmented macule on the right calf were recorded. Karyotyping disclosed reciprocal translocation between 16 and 17 chromosomes, further genetic analysis is planned. The parents were suggested to observe for subtle seizure manifestations. Complex partial seizures were noted at the age of two months, lasting for 5–60 seconds, up to15 seizures per day. Psychomotor slowing, muscle hypotonia, reduced movements of the left extremities were observed. EEG showed fragments of hypsarrhythmia. Immediate treatment with vigabatrin 500 mg/day controlled seizures for 3 weeks, later steroids were added to control relapse.

CONCLUSION. This case shows an extremely early and severe manifestation of TSC and the importance of early diagnosis. Careful follow-up management is essential, and the role of mTOR inhibitors deserves discussion.

Do methylenetetrahydrofolate reductase (*MTHFR*) polymorphisms raise homocysteine levels in children with migraine? May B vitamins help?

Anna-Liisa Lorenz[1], Eve Õiglane-Shlik[2], Tiina Kahre[3], Tiit Nikopensius[4], Evelin Mihailov[4], Andres Metspalu[4], Anneli Kolk[2] – [1]University of Tartu, Genetic Engineering, Estonia; [2]Department of Child Neurology, Children's Clinic, Tartu University Hospital, Tartu, Estonia; [3]Department of Genetics, United Laboratories, Tartu University Hospital, Tartu, Estonia; [4]University of Tartu, Estonian Genome Center, Estonia

INTRODUCTION. Decreased activity of enzyme methylenetetrahydrofolate reductase (MTHFR), which is caused by the common polymorphisms C677T and A1298C, is considered to cause the accumulation of homocysteine. Folate and B12 are necessary for catalysation of homocysteine (Hcy), whereas deficiencies in those cofactors can cause hypomethylation, which is presumed to trigger migraine.

The aim of the study was to examine the role of folate, B12 and *MTHFR* polymorphisms on Hcy level in children having migraine with and without aura.

METHODS. Altogether 92 pediatric migraine patients (F = 53, M = 39) participated in the study. 36 patients had migraine with aura (F = 24, M = 12) and 56 had migraine without aura (F = 29, M = 27). DNA testing for both polymorphisms was performed; genotypes were determined by PCR using specific primers. Hcy, folate and B12 levels were measured at the United Laboratories of Tartu University Hospital. Statistical analysis was performed using the PL INK software.

RESULTS. The average homocysteine level was higher in patients, both with (10 ± 3.7 µmol/L) and without aura (9.2 ± 3.0 µmol/L), compared with mean reference concentration (average 6 µmol/L). Higher Hcy concentrations were significantly associated with defective 677T ($p = 0.003$), but not with 1298C ($p = 0.7$) alleles. Patients with aura showed stronger evidence of association ($p = 0.028$) than patients without aura ($p = 0.07$).

Vitamin B12 and folate mean concentrations were within normal ranges.

Sixteen patients passed remeasurement of Hcy after receiving B-vitamin and folate supplementation; homocysteine concentration had decreased in 11 patients.

CONCLUSION. Increased homocysteine levels are associated with 677T allele, which can lead to higher risk for migraine. B-vitamin and folate supplementation seems to be justified for reducing high homocysteine levels; therefore, it could be an effective method for relieving migraine symptoms.

An interstitial deletion of chromosome 7q35q36.1 in a 3-year-old boy with clinical features of Weaver syndrome

Laura Roht[1], Karit Reinson[1], Inga Talvik[2,3], Riina Žordania[1], Kati Kuuse[1], Olga Žilina[1,4], Katrin Õunap[1,3] – [1]Department of Genetics, United Laboratories, Tartu University Hospital, Tartu, Estonia; [2]Children's Clinic, Tartu University Hospital, Tartu, Estonia; [3]Department of Paediatrics, University of Tartu, Tartu, Estonia; [4]Department of Biotechnology, Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia

The phenotype of *EZH2*-related overgrowth, known as Weaver syndrome, usually incorporates tall stature, variable intelligence, advanced bone age (100%), poor coordination, soft doughy skin, camptodactyly, umbilical hernia, a hoarse low cry in infancy. Facial characteristics may include macrocephaly, broad forehead, round face, large fleshy ears, hypertelorism, almond-shaped eyes and retrognathia. Most cases of Weaver syndrome are sporadic and caused by heterozygous mutation in the *EZH2* gene on chromosome 7q36.

The aim is to present a case report of a 3-year-old boy first investigated because of speech delay. His birth weight was 5080 g (> + 2 SD), length 53 cm (0 SD) and head circumference 39 cm (> + 2 SD). In the early neonatal period he had an episode of hypoglycemia. At the age of 3 years his head circumference was rather large (+2 SD) but his height was normal (102 cm, + 0.5 SD). He had mild dysmorphic features - round face, large fleshy ears,and speech delay, which could be the evidence of intellectual disability. At present, his bone age was not advanced. Chromosomal microarray analysis (Human CytoSNP-12 BeadChip, Illumina Inc.) revealed a 3Mb *de novo* interstitial deletion on the paternal chromosome in bands 7q35q36.1. The region contained 2 disease-related genes: *CNTNAP2* and *EZH2*.

CONCLUSION. In this case report we present a patient who has some clinical features of Weaver syndrome and rare 7q35q36.1 microdeletion. This is a very rare microdeletion.

NEUROGENETICS

The mTOR system and neurology

Milda Endzinienė – Lithuanian University of Health Sciences, Kaunas, Lithuania

The mammalian target of rapamycin (mTOR) regulates a number of physiological functions including cell growth, proliferation, metabolism, protein synthesis and autophagy. Within the nervous system, mTOR is involved in synaptic plasticity and cortical development. In tuberous sclerosis complex (TSC), abnormal mTOR signaling promotes the progression of subependymal giant cell astrocytoma (SEGA), renal angiomyolipomas (AML) and other hyperplasias, and mTOR inhibitors have shown their positive inhbitory effects on this proliferative process. The effect of mTOR inhibitors in cases of gliomas seems encouraging, possibly for their antiproliferative and antiangiogenetic mechanism, thus leading to increased sensitivity to radiation and decreased invasive propensity. Animal models of TSC and clinical trials targeted to SEGA and AML treatment in TSC have shown evidence of antiepileptogenic effects of mTOR inhibitors. The data regarding direct effects of mTOR inhibitors in the treatment or prevention of epilepsy is still lacking although the influence on neurone sprouting and synaptogenesis may be the possible mechanisms of antiepileptic effects in structural epilepsies following acquired brain injury or certain mTOR-related genetic predisposition (like megalencephaly or cortical dysplasia type II which may have pathophysiological and cellular abnormalities similar to TSC). The mTOR pathway seems to be involved in the learning process and thus may be responsible for the development of autism or mental retardation, at least in some genetic disorders, like Down, Rett and Fragile X syndromes. The mTOR pathway is possibly involved in the development of Alzheimer`s, Parkinson's and Huntington diseases. Further research may lead to better treatment options with mTOR inhibitors in an even broader spectrum of chronic progressive neurological disorders.

Tuberous Sclerosis Complex: an update on neurological aspects

Rima Nabbout – Reference Centre for Rare Epilepsies and Tuberous Sclerosis Complex, Department of Pediatric Neurology, Necker Hospital, University Paris Descartes, Paris, France

Tuberous sclerosis complex (TSC) is a rare genetic disorder characterized by the development of benign tumors across several organs. The diagnosis of TSC is made based on the presence of certain major and minor criteria, which were recently revised at the 2012 International TSC Consensus Conference. Mutations in either *TSC1* (hamartin) or *TSC2* (tuberin) gene are identified in approximately 85% of the patients. These result in constitutive activation of the mammalian target of rapamycin (mTOR) complex 1, which is a key regulator of cell growth and proliferation.

For patients with antenatal or presymptomatic diagnosis in infancy, follow up should provide early detection of electric and clinical seizures in order to initiate AEDs. Epilepsy could manifest by focal seizures and/or infantile spasms. Vigabatrin is the treatment of choice and in case of failure, steroids and ketogenic diet should be proposed. Surgery should be considered in all patients and should be performed by a team dedicated to childhood epilepsy surgery. Successful treatment of infantile spasms can improve the overall cognitive prognosis. The role of mTor inhibitors in the treatment of epilepsy is actually being evaluated in a placebo controlled trial.

Subependymal giant cell astrocytomas (SEGAs), the major cause of death and comorbidities in childhood, should be monitored with regular imaging. Growing SEGA is an indication for therapy which should be performed before the onset of intracranial hypertension signs and symptoms. Treatment of SEGA could be surgical or with mTor inhibitors depending on the tumor volume and number, the emergency setting, the association of other benign tumors and the neurosurgeon expertise.

TSC-associated neuropsychiatric disorders (academic/scholastic difficulties, autism spectrum disorder, attention deficit hyperactivity disorder, depressive disorder, and anxiety disorder) are frequently reported when carefully checked and should be carefully followed in patients with neurological involvement.

Tuberous Sclerosis Complex: Situation in Estonia

Valentin Sander[1], Inga Talvik[2,3] – [1]Tallinn Children's Hospital, Tallinn, Estonia; [2]Department of Pediatrics, University of Tartu, Tartu, Estonia; [3]Children's Clinic of Tartu University Hospital, Tartu, Estonia

TSC complex is a rare disease caused by two different gene mutations – TSC1 and TSC2. Despite its „orphan disease"status, this condition is well known among pediatric neurologists and, in case of a typical phenotype, easily recognized. Nevertheless, 15 known cases of TSC among pediatric population (260 000) is remarkably less than expected (26).

Only one diagnosis of TSC out of 15 was made by a geneticist after cardiac surgery in the first month of life and in one case TSC was first suspected by dermatologists. In one case this condition was suspected prenatally in a mother suffering from tuberous sclerosis.

All diagnoses of TSC were made/revised according to the recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Genetic testing was performed in five patients. All main clinical features of TSC are present in our cohort, except for LAM.

The patients are regularly followed up to find possible tumors. One patient needed both SEGA and AML surgery. Two patients are on long-lasting everolimus treatment.

At present, the major challenge is how to transfer these patients to the adult health care system because of various clinical manifestations of this condition at that age.

Estonia is currently participating in the International TOSCA project with two sites and 12 patients for a better quality of life of the TSC community.

Latvian experience: The efficiency of everolimus in tuberous sclerosis patients with subependymal giant cell astrocytoma (SEGA)

Diāna Volčeka[1,2], Gundega Lipsberga[1], Sarmite Dzelzite[2,3], Guntis Rozentals[2] – [1]Riga Stradins University, Riga, Latvia; [2]Children's Clinical University Hospital, Riga, Latvia; [3]University of Latvia

INTRODUCTION. Tuberous sclerosis complex (TSC) is a highly variable disease and can affect any organ in the body. Its frequency is 1 per 6000–10000 live births, and prevalence is 1 case per 10000. TBS is an autosomal dominant disease with incomplete penetrance and variable expression; 50–80% is sporadic mutations. Mutations occur in either of two genes TSC1 (19q34 chromosome) and TSC2 (16p13chromosome). TSC codes the protein hamartin, TSC2 codes tuberin. These proteins form a tumor suppressor complex; hence they regulate cell proliferation and differentiation. Deficit of this protein results in multiple hamartomous tumors, that usually affect skin, brain, heart, kidneys, eyes, lung and bones. Neurological findings compricse cortical tubers (90%), subependymal nodules (SENs, 90%) and subependymal giant cell astrocytoma (SEGAs, 5–15%). Clinical manifestation is variable, from severe mental retardation and disabling seizures to normal intellect.

Medical management with Everolimus (Rapamycin-derivate kinase inhibitor, reduces cell proliferation and angiogenesis by inhibition of the mTOR pathway) is associated with marked reduction in the volume of SEGA, seizures frequency and improvement in the quality of life.

METHODS. This is a prospective research and we published our experience with the first patient in Latvia who received Everolimus.

RESULTS. A 9-year-old girl was diagnosed with tuberous sclerosis when she was 6 months old. She is severely mentally retarded, autistic and suffers from symptomatic epilepsy with common partial seizures. On the facial skin she has *café au lait* spots, multiple angiofibromas and Shagreen's patches. She has multiple hamartomas in the kidneys and angiofibromas in the liver.

MRI scans of brain (16 July 2013) Conclusion: tuberous sclerosis with multiple subcortical tubers, subependimal hamartomas and with SEGA in the left brain ventricle. In the foramen Monroe region there is a large subependimal astrocitoma, with axial size 2.8x2 cm, craniocaudal 2.5cm, the other astrocitoma is smaller, 1.5x1.5x1.6cm, diameter 0.6cm. Decision of neurosurgical consultation: surgical treatment would be less efficient as resection of one tumor node will not improve the patient's

condition; initiation of treatment with *Everolimus* 5 mg once per day from 4 April 2014.

On 20 November 2014 repeat MRI scan. Conclusion: The largest astrocitoma is reduced (former diameter approximately 3 cm, present diameter 2 cm), the other astrocitoma has also reduced (from 1.5 cm to 1.3 cm).

Since the girl started receiving *Everolimus* the number of seizures has decreased significantly and her mental state has improved. She still takes *Everolimus* 10 mg per day and is under medical supervision.

CONCLUSION. We gained positive experience with Everolimus usage. Treatment with Everolimus in TSC patients with SEGA reduces the volume of subependimal astracitomas, improves the patient`s mental state and often also seizures.

Everolimus in young patients with tuberous sclerosis complex

Lingvita Gumbelevičienė[1], Kristina Zaveckienė[1], Milda Endzinienė[1,2] – [1]Neurology Department, Hospital of Lithuanian University of Health Sciences, Kaunas, Lithuania; [2]Lithuanian University of Health Sciences, Kaunas, Lithuania

INTRODUCTION. Tuberous sclerosis complex (TSC) is characterized by non-malignant tumors in different organs, which can provoke life-threatening complications. The mammalian Target of Rapamycin (mTOR) inhibitor everolimus is a new treatment option for patients with TSC, which can help avoid surgical treatment and dangerous consequences of these tumors.

CASE REPORTS. We present the cases of three young girls with TSC who have been treated with everolimus for 2 years. The first case is a 17-year-old girl who had surgical treatment because of rabdomyoma (at the age of 9 years) and subependymal giant cell astrocytoma (SEGA) (at the age of 9 and 10 years). Before initiation of everolimus therapy she had SEGA regrowth, multiple renal and liver angiomyolipomas (AMLs), cardiac rhabdomyomas, adenoma sebaceum. Reduction in SEGA and renal AMLs was noted after 3 months of treatment. Further, a reduction in rabdomioma volume, less expressed adenoma sebaceum, improvement in memory and attention were noted. She experienced transient stomatitis, acne, hypercholesterolemia, hypertriglyceridemia within the treatment period. The second case is a 14-year-old patient in whom everolimus therapy was initated because of growing AML and deteriorating renal function. There was a marked decrease in the size of renal AMLs, reduction in adrenal adenoma, and improvement of adenoma sebaceum. Transient diarrhea was noted during the titration period. The third case is a 19-year-old patient for whom everolimus was prescribed because of renal, liver AMLs and SEGA, as well as handicapping daily headaches unresponsive to analgesics or acetazolamide. Treatment with everolimus resulted in decreasing or stabilisation of all tumors in size, disappearance of daily headaches, and less expressed skin angiofibromas. Transient vomiting and dysmenorrhea (requiring treatment) were observed within the treatment period.

CONCLUSION. Our case reports suggest that treatment with everolimus may lead to reduction or stabilization of tumor growth without any serious adverse effects.

Levodopa responsive dystonia in children

Jolita Urbonaitė, Nerija Vaičienė-Magistris, Milda Endzinienė – Neurology Department, Medical Academy and Hospital of Lithuanian University of Health Sciences; Kaunas, Lithuania

BACKGROUND. Levodopa responsive dystonia (LRD) is a condition characterised by the onset of dystonia in early childhood with sustained response to treatment with levodopa. The disorder was first described by Segawa who named it hereditary progressive dystonia with marked diurnal fluctuation. High index of suspicion is required as an incorrect diagnosis of this potentially treatable disease leads to physical dissability and social restrictions.

CASE PRESENTATION. We present four cases of LRD in children diagnosed in our department over the years. All cases presented in early childhood with non-specific symptoms such as rapid fatigue, clumsiness, gait abnormalities. Later on, all of them developed posturing of extremities with progressive walking difficulty. In 3 cases, the function of the hands was impaired as well. LRD was diagnosed after 1 (2 cases), 8 and 10 years of the appearance of initial symptoms. Two girls were diagnosed as having cerebral palsy, one of them underwent orhopedic surgery of the ankle. Clinical examination revealed brisk tendon reflexes, posturing of the extremities, „striatal toe" (pseudo-Babinski sign) and diurnal variation of symptoms. Levodopa dramatically reduced or abolished symptoms after a few days of the start of the treatment. Skipping levodopa worsened clinical symptoms and necessitated the parents to use continuous treatment.

CONCLUSION. LRD should be suspected in any case of dystonia or „progressive cerebral palsy" irrespective of duration of the disease, especially when symptoms fluctuate during the day. All patients with childhood or early adulthood dystonia should undergo a trial with levodopa even when clinical signs are not specific of LRD.

The first deep brain stimulation in Lithuania for generalized dystonia in a teenager

Nerija Vaičienė-Magistris[1], Jurgita Karandienė[1], Andrius Radžiūnas[2] – [1]Neurology Department, Medical Academy and Hospital of Lithuanian University of Health Sciences, Kaunas, Lithuania; [2]Neurosurgery Department, Medical Academy and Hospital of Lithuanian University of Health Sciences, Kaunas, Lithuania

INTRODUCTION. Primary torsionic dystonia is a rare genetic disease characterized by involuntary sustained muscular contractions that lead to abnormal postures and repetitive movements of one or several parts of the body. Neurostimulation of internal globus pallidus is the most effective treatment in reducing symptoms of primary dystonia.

CASE. We present a 16 year-old boy with a 9-year history of primary generalized torsionic dystonia. Various investigations ruled out symptomatic dystonia. Genetic investigation excluded mutation in the DYT1(TOR1A) gene. Symptoms started at the age of 7 years as involuntary painful contractions in the left hand and right leg, later contractions involved all extremities, and the neck and trunk, causing difficulty to walk and scoliosis which has been corrected by orthopedic surgery. During the 8-year period the disease slowly progressed with rapid worsening at the age of 15 when painful dystonic movements in the legs and pelvis developed, the patient lost his ambulation, was suffering from severe pain and became bedridden. Various pharmacological agents were used (including L-dopa) without an effect. In October 2014 deep brain stimulation (DBS) implantation was performed at the Department of Neurosurgery in Kaunas, using the St. Jude Medical DBS system. Two leads with 4 contacts and 1.5mm spacing were stereotactically implanted bilaterally in globus pallidus internus, followed by control of the lead position using intraoperative CT with Ceretom™. Afterwards 1.5T MRI was performed to visualize the lead position directly in Gpi. On the same day a Brio™ rechargeable impulse generator was implanted, and since that time the patient has been able to cooperate; monopolar constant current stimulation was started with 130 Hz and 60 ms settings. DBS resulted in a dramatic positive effect: the patient immediately became free of painful contractions; in one week he was able to sit without support and to stand up. At five months of follow-up he is able to walk and run as well as to attend school and to live a normal social life.

CONCLUSION. DBS has a long-term effect for primary dystonia, which leads to a marked reduction in physical disability and improvement of both the patient‘s and family`s quality of life; the treatment method has to be considered and performed without delay.

EPILEPSY

Classification of the epilepsies: Old and new with relevance to clinical practice & epidemiological studies

J Helen Cross – UCL-Institute of Child Health, Great Ormond Street Hospital for Children, London; National Centre for Young People with Epilepsy, Lingfield, UK

Classification is not new. The initial classification of the epilepsies was proposed by Gastaut in 1969 (1). Since then, the classifications have been updated for seizures (1981) (2) and syndromes (1989) (3) with minimal changes. The purpose of the classification was to provide a common language and set of concepts to facilitate communication about research and treatment, and certainly this is how it has been utilised over subsequent years. In 2001, the Task Force on Classification and Terminology reported on a further proposal, taking into consideration confusion that had arisen in the use of some of the terminology, acknowledging it had led to un-necessary complexity. They also proposed approval of a diagnostic scheme rather than a fixed classification, with further definition of terminology and acknowledgement of the better accepted syndromes (4), stating 'epileptic seizures and epilepsy syndromes are to be described according to a system that uses standardised terminology'. However with time, with an increasing list of recognised syndromes and progress in research, there has been a need to incorporate information from more sophisticated investigative techniques. This aside, it is important to retain a system that is widely applicable, and utilising a common language.

Over the four year term 2005–2009, the ILAE Commission for Classification attempted to address the problem modernising the classification (5). This was not to replace existing models totally, but to contribute to ease of use. Further it tried to take into consideration the ever changing playing field of imaging and genetics. Confusing terms with regard to seizure description were removed. The terms focal and generalised in the majority refer to seizures. Syndromes should be diagnosed on the basis of age of onset; the existing lists of syndromes remain. However the terms idiopathic and symptomatic are no longer recommended; syndromes will now be classified into genetic (or presumed genetic), structural/metabolic (since further subdivided into structural, metabolic, immune and infectious) or unknown. Of course some age related syndromes may fit into any of these categories. Further, of relevance to paediatrics, the term epileptic encephalopathy has been redefined as a

concept that may apply to any individual with epilepsy, accepting those with certain syndromes will be more at risk than others, rather than only applying to a small number of the more complex syndromes. The move is toward a description of the epilepsy, to allow a practical pragmatic approach to diagnosis.

Although this classification has been proposed, it is very much work in progress with plans to take the situation further forward in the future. A recent refinement of the proposal to ease utilisation has recently been available for comment. Further a diagnostic has been made available at www.EpilepsyDiagnosis.org.

REFERENCES

1. Gastaut H. Classification of the epilepsies. Proposal for an international classification. Epilepsia 1969;10:Suppl:14–21.
2. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1981;22:489–501.
3. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1989;30:389–99.
4. Engel J Jr. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the ILAE task force on classification and terminology. Epilepsia 2001;42:796–803.
5. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organisation of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 2010;51:676–85.

Consciousness and epileptic seizures: where are we?

Walter van Emde Boas – Department of Clinical Neurophysiology, SEIN - Epilepsy Institute in The Netherlands, Meer en Bosch, The Netherlands; Department of CNP at the Free University Medical Center, Hoofddorp, The Netherlands; Department of Neurosurgery at the Free University Medical Center, Hoofddorp, The Netherlands

"Impairment of consciousness" is considered to be a main characteristic of many epileptic seizures, yet the subject remains controversial and concepts and definitions have changed significantly during the past decades.

In many seizures, notably temporal lobe seizures with automatisms and, in absence type "generalised" seizures, impairment of consciousness was more or less automatically assumed (and implied in the then current definitions) yet with the increased application of EEG/Video seizure monitoring it became clear that this was often not the case.

Analysis of these videos and testing of the patient revealed that often there was no impairment at all or there was impairment only of specific functions, resulting in the concept of dyscognitive features that could be identified as separate "semiological" signs and symptoms. A further step was abandoning the issue of consciousness as a classifying feature of seizures, despite the fact that this feature has significant effects on psychosocial impairment associated with epilepsy, and hence it was considered a major differential issue for most clinicians. Therefore, in the latest "Proposal for the organisation of seizures and epilepsies" the concept of dyscognitive seizures is reintroduced in a different sense as originally proposed in the "Glossary" of semiological signs and symptoms, leading to renewed controversy and discussions about this terminology and how to use it. The issue is further complicated since the terms such as "Consciousness", "Awareness" and "Cognition" have different meanings in different disciplines (neurologists, neuropsychologists, philosophers). Even within the narrower limits of neurology and clinical neuropsychology it can only be assessed to a limited extent during brief events such as epileptic seizures. A summary of these developments and the current status will be presented.

Treatment of patients with Dravet syndrome

Rima Nabbout – Reference Centre for Rare Epilepsies, Department of Pediatric Neurology, Necker Hospital, Paris, France; University Paris Descartes, Paris, France

Dravet syndrome (DS) is a rare epilepsy syndrome with an onset before age 1 year. First seizures are mainly clonic or tonic–clonic, long lasting and unilateral. Later on, other seizure types appear (myoclonia, atypical absences and focal seizures). Fever is a triggering factor, apart from external heat and exercise. Developmental retardation develops around age 2 years and definite cognitive impairment, behavior and personality disorders are noted at age 4–5 years. SCN1A gene defect is the major cause of this syndrome (80%).

Valproate (VPA) is the first AED prescribed in DS, usually associated with benzodiazepines: clonazepam (CZP) or clobazam (CLB). Stiripentol (STP) is the only authorised AED in DS in adjunction with VPA and CLB. STP has proven useful in decreasing the frequency and duration of convulsive seizures and the number of status epilepticus. Topiramate (TPM) is used in controlling convulsive and focal seizures. Other AEDs are prescribed for adjunctive therapy, e.g. Bromide, Levetiracetam, Ethosuximide and Zonisamide. Some AEDs might worsen seizures: carabamazepine, lamotrigine and vigabatrin. The efficacy of ketogenic diet (KD) in DS has been reported in several series. Epilepsy surgery is not recommended and vagus nerve stimulation (VNS) can be an option to improve QOL.

Patients with DS present several comorbidities. They should undergo periodic cognitive evaluation in order to individualise the delayed milestones and to offer appropriate educative methods: psychomotricity, speech therapy, psychological support. Management of behavioural disorders and psychological support is a major issue. Sleep disorders not only due to nocturnal/sleep seizures and prescription could benefit from sleep inducers. Other specific cares address regular physiotherapy and psychomotricity for motor impairment; orthopaedic consultation for cyphoscoliosis and foot deformities, especially in adult life, and counselling with a nutritionist for feeding difficulties (chewing/swallowing difficulties, lack of appetite).

New promising AEDs as Cannabidiol (CBD) and Fenfluramine are being considered. CBD is the major nonpsychoactive ingredient in cannabis and a double-blind randomized, controlled study was launched in EU and the USA. Fenfluramine was used in a small series (12 patients) and showed high efficacy (70% seizure-free). A controlled study is planned. Cognitive outcome, in addition to seizure response, should be considered in further trials.

The risks and benefits of valproate

Eija Gaily – Children's Hospital, Helsinki University and Helsinki University Hospital

A warning was issued recently by The European Medicines Agency that due to its teratogenic effects, valproate should not be used in female children, women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated. This is of concern to pediatric neurologists as valproate is one of the major drugs used in treating pediatric epilepsy.

Based on recent major prospective registry studies, fetal exposure to valproate monotherapy is associated with a significantly increased risk of major congenital malformations when compared to children exposed to carbamazepine, or lamotrigine *in utero*. The teratogenic effect of valproate appears to be dose-related; daily doses not exceeding 600 mg are not significantly different from carbamazepine over 500 mg/day or lamotrigine over 300 mg/day. Reported outcomes after levetiracetam exposure are not alarming but the numbers are relatively small. Data on topiramate or oxcarbazepine are very scarce.

Valproate is also associated with functional teratogenicity. Prospective registry studies have reported a significant IQ reduction (average 7–11 points) in valproate-exposed children compared to children exposed to carbamazepine, lamotrigine or phenytoin. Also this effect seems to be dose-related; IQ outcomes after exposure to less than 800–1000 mg/day are similar to those for the other studied drugs. Prenatal exposure to valproate has also been associated with an increased risk of autistic spectrum disorder. Data on functional teratogenicity of all other AEDs are insufficient.

The efficacy of valproate against primary generalized tonic–clonic, myoclonic and absence seizures has been shown by randomized controlled trials (RCT), but no syndrome-specific RCTs have been conducted except for childhood absence epilepsy (CAE). The double-blind trial included 453 children with newly diagnosed CAE and compared valproate, ethosuximide and lamotrigine. Valproate was found to be more effective than lamotrigine and equally effective with ethosuximide, while ethosuximide was better tolerated.

For focal seizures in general, current evidence do not support using valproate as a first line treatment. In children, focal seizures may arise in the context of certain childhood epilepsy syndromes, such as epilepsy with continuous spike –waves during sleep (CSWS or ESES syndrome), atypical benign focal epilepsy and Dravet syndrome. In these conditions,

valproate is an appropriate first choice for treating focal seizures and other seizure types, as sodium channel blockers, such as carbamazepine, oxcarbazepine or lamotrigine may exacerbate both seizures and neurocognitive dysfunction.

For defined pediatric epilepsy syndromes other than CAE, only observational data on treatment are available. Based on these reports and expert concensus, valproate may be considered as an appropriate initial treatment for myoclonic epilepsy in infancy, atypical benign focal epilepsy, eyelid myoclonia with absences, epilepsy with myoclonic absences, epilepsy with myoclonic atonic seizures, epileptic encephalopathy with continuous spike-and-wave waves in sleep, including Landau-Kleffner syndrome, Dravet syndrome and Lennox-Gastaut syndrome. In progressive myoclonic epilepsies, valproate must be used with caution; because of the risk of fatal liver failure, it is contraindicated in some mitochondrial disorders, especially those with *POLG* mutations.

Valproate remains an important drug in the treatment of many pediatric epilepsy syndromes. Teratogenic concerns are minor in syndromes such as childhood absence epilepsy which have a high likelihood of remission and treatment withdrawal before puberty. Valproate may also be used as initial treatment for children regardless of gender when the epilepsy and concurrent disabilities are so severe that future pregnancy is extremely unlikely. For adolescents with new onset idiopathic (genetic) generalized epilepsy, valproate should be considered as an initial treatment as it may be more effective than other drugs. As in the case of AED treatment in general, the lowest effective dose should be prescribed, especially when valproate is selected for an adolescent girl.

REFERENCES

- Baker GA, Bromley RL, Briggs M, et al. IQ at 6 years following in utero exposure to antiepileptic drugs: a controlled cohort study. Neurology 2015;84:382–90.
- Christensen J, Gronborg TK, Sorensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA 2013;309:1696–703.
- Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid and lamotrigine in childhood absence epilepsy. N Engl J Med 2010;362:790–9.
- Hernandez-Diaz S, Smith CR, Shen A, et al. Comparative safety of antiepileptic drugs during pregnancy. Neurology 2012;78:1692–9.
- Meador K, Reynolds MW, Crean S, et al. Pregnancy outcomes in women woth epilepsy: A systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res 2008;81:1–13.
- Tomson T, Battino D, Bonizzoni E, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol 2011;10:609–17.
- Wheless JW, Clarke DF, Arzimanoglou A, et al. Treatment of pediatric epilepsy: European expert opinion, 2007. Epileptic Disord 2007;9:353–412.

Cannabinoids for the treatment of epilepsy

J Helen Cross – UCL-Institute of Child health, Great Ormond Street Hospital for Children, London & Young Epilepsy, Lingfield UK

There has long been discussion as to whether Cannabis may be effective in the treatment of epilepsy, with evidence it could be anti or proconvulsant. However emerging evidence suggests cannabinoids, such as cannabidiol, with minimal Δ^9 Tetrahydrocannabinoid (Δ^9THC, the psychoactive component) may be effective. Four randomised controlled trials exist in the literature. However there were various methodological issues, not least the relatively small sample size, and very little in the way of conclusions could be drawn. A recent Cochrane review (2014) commented no reliable conclusions could be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy. Interest however has been rekindled, initially through own formulated preparations in young children with complex epilepsy, and more recently in open label trials of epidiolex (GW Pharma). Early data show promise; however we await the results of efficacy and safety from randomised controlled trials in Dravet syndrome and Lennox Gastaut syndrome.

Non-pharmacological treatment of epilepsy: Estonian experience

Ulvi Vaher[1], Valentin Sander[2] – [1]Children's Clinic of Tartu University Hospital, Tartu, Estonia; [2]Tallinn Children's Hospital, Tallinn, Estonia

About 20–30% of people with epilepsy continue to have seizures despite appropriate antiepileptic drug treatment. Childhood epilepsies present a broad group of disorders with developmental, behavioural and cognitive comorbidities. The adverse effects of seizures on the developing brain should raise the priority of freedom from seizures.

Children who have failed two or more anticonvulsant drugs should be considered for surgical or ketogenic diet therapy.

Since 2010 epilepsy surgery has been performed for 6 patients aged 2 to 15 years, among whom five have been completely seizure free after surgery. The etiologies of these patients were: cortical dysplasia in 2, low grade tumors in 3 and Rasmussen encephalitis in one. Ketogenic diet has been implemented for five children: one with success, two with partly reduced seizures.

We report the patients' clinical data and outcome and discuss local possibilities and future perspectives.

Atypical idiopatic focal epilepsies with centrotemporal spikes: from clinical features to fMRI

Ruta Samaitienė – Clinic of Children's Diseases, Faculty of Medicine, Vilnius University; Department of Children`s Neurology, Children's Hospital, Affiliate of Vilnius University Hospital Santariskiu Clinics, Vilnius, Lithuania

Benign epilepsy with centrotemporal spikes (BECTS) is age-specific idiopathic epilepsy syndrome of childhood. BECTS is a heterogeneous entity with many atypical forms. Learning, language, and behavioral problems, specific transient cognitive deficits in the active phase and EEG spike-wave discharges activation in BCECTS cases have been described. Consensus definition on atypical forms of BECTS is still lacking. These cases have been called various names as BECTS plus conditions, Rolandic epilepsy spectrum disoders, Rolandic epilepsy related disorders.

It is important to discriminate between atypical features of BECTS and atypical evolution of benign focal epilepsies. Atypical features mean benign prognosis as in typical BECTS. Atypical evolution indicates disorders related to continuous spike-and-waves during slow sleep (CSWS). Atypical benign partial epilepsy (ABPE) is one of these conditions and it will be discussed more in detail. The exact genetic basis of these conditions is unknown. New heterozygous mutations were detected in GRIN2A in patients with idiopatic focal epilepsy with rolandic spikes. Mutations occurred significantly more frequently in patients with CSWS than in patients with BECTS.

The localization of the sources of magnetoencephalography (MEG) spikes shows that ABPE presents with Rolandic-sylvian onset seizures. Possible thalamo-cortical epileptic networks are hypothesised. FMRI studies demonstrated that children with BECTS had functional changes, more atypical language networks compared to healthy controls. FMRI investigation showed that ABPE is characterized by patterns similar to those found in studies of rolandic epilepsy as well as by patterns observed in CSWS. These studies show that idiopathic focal epilepsies of childhood form a spectrum of overlapping syndromes.

The genetic revolution in childhood epilepsy: also evolution to better care?

Lieven Lagae – University Hospitals KULeuven, Leuven, Belgium

In the last years, we have observed a revolution in the understanding of the genetic causes of childhood epilepsy. More and more mutations in different genes are described as the cause of many epilepsy syndromes. However, in clinical practice it is not always clear how helpful this is for an individual patient. Many questions have remained unsolved. For instance: How can the same mutation cause a benign epilepsy syndrome in one patient and an epileptic encephalopathy in another patient (see SCN1A and KCNQ2). Are the described mutations always pathogenic or only variants? Even if we understand the genetic basis of epilepsy, does it help us in designing better treatments? Is it still defendable to test for a single gene mutation in a particular phenotype or should we immediately move over to gene panels or whole exome sequencing? It seems crucial that, more than ever, clinicians continue to describe the individual patient as well as possible, including seizure characteristics, MRI and EEG data, to obtain better correlation with genetic findings.

TEACHING COURSE III: PERINATAL STROKE

Perinatal stroke: Mechanisms of injury and outcomes

Adam Kirton – Calgary Pediatric Stroke Program, Alberta Children's Hospital Research Institute, Departments of Pediatrics and Clinical Neurosciences, University of Calgary, Calgary, Canada

Perinatal stroke accounts for most hemiparetic cerebral palsy with additional lifelong neurological morbidity in many survivors. Modern neuroimaging can now define specific perinatal stroke diseases including symptomatic neonatal arterial ischemic stroke, fetal and presumed perinatal strokes such as periventricular venous infarction, neonatal cerebral sinovenous thrombosis, and neonatal hemorrhagic stroke. Imaging diagnosis and evaluation of risk factors will be reviewed. Acute management options including neuroprotection, seizure control, and the role of anticoagulation therapy will be addressed. Long-term outcomes common across the perinatal stroke diseases including sensorimotor disability, developmental disorders, and epilepsy will be reviewed including current and emerging rehabilitation interventions.

EPILEPSY GENETICS

Mechanisms and therapeutic consequences of genetic epilepsies

Holger Lerche – Department of Neurology and Epileptology, Hertie-Institute for Clinical Brain Research, University of Tuebingen, Tuebingen, Germany; Werner Reichardt Centre for Integrative Neuroscience, Tuebingen, Germany

Our goal is to identify the underlying common and rare genetic causes and risk factors of epilepsies, and to translate important findings into the best practice care for the patient`s benefit. Most recent findings point out an increasing number of individual therapies for defined monogentic epilepsy syndromes. Namely, Glut1 defects are treated with ketogenic diet; Na channel blockers are not recommended for SCN1A defects but seem to be beneficial in SCN2A and KCNQ2 defects; quinidine is beneficial in KCNT1 defects and memantine is beneficial in some NMDA receptor defects, to list a few recent examples. Zebrafish screening studies are, moreover, able to find new therapies for not readily treatable epilepsies, as the first examples show for SCN1A defects. In addition, there is hope that pharmacogenetics will bring about results regarding which drugs might be beneficial in individual cases of common epilepsies. A first genetic marker can prevent severe cutaneous reactions to carbamazepine in South Asian populations. The report will focus on the mechanisms that are important for therapy and that can bridge clinical results with research findings in a comprehensive way.

Genetics of epilepsy: what recent discoveries have taught us

Sarah Weckhuysen – Neurogenetics Group, Department of Molecular Genetics, VIB, Antwerp, Belgium

The advent of a next generation sequencing techniques has revolutionised epilepsy genetics research. The rate of gene discovery has rapidly increased over the last few years, and especially in the field of epileptic encephalopathies new genes are being discovered at a steady pace. Genetics is offering us novel insights into the range of the pathomechanisms underlying epilepsy, and is paving the way towards personalized medicine.

Using some recent gene discoveries as an example, this report will illustrate both our advances in understanding and use of targeted treatments in genetic epilepsies.

Algorithms for epilepsy genetic testing

Birute Tumienė[1,2], Algirdas Utkus[1,2] – [1]Vilnius University, Faculty of Medicine, Department of Human and Medical Genetics; [2]Vilnius University Hospital Santariškių Clinics, Centre for Medical Genetics

Genetic factors play a major role in many epileptic conditions. The main diagnostic genetic testing approaches used are chromosomal analyses/molecular karyotyping; candidate gene testing; biochemical genetic testing; gene panels; and whole-exome/whole-genome sequencing. Taking into consideration all current benefits, limitations and presumable outputs of these methods, it is of major importance to use proper genetic testing algorithms for maximizing benefit and minimizing harm to epilepsy patients.

Molecular karyotyping should be the first-tier diagnostics for patients with developmental disabilities/congenital malformations. In epilepsy patients, it yields additional 7–20% to traditional karyotyping, the biggest outputs being observed in epilepsy plus comorbidities (intelectual disability/autism/congenital malformations/dysmorhism).

Candidate gene testing is most suitable in situations of highly specific phenotypes pointing to relatively homogenous genetic etiologies. However, genetic heterogenity still remains even in these cases and screening of one gene after another is a slow, costly and sometimes even an impossible process. Biochemical genetic testing can still be of value, especially in the diagnostics of specifically-treatable IEMs.

Gene panel testing has emerged as a highly useful method for testing epilepsies with limited specificity of phenotype, extensive genetic heterogeneity and common etiological mechanisms. Whole-exome sequencing (WES) with later application of gene panels was applied as a means to partially overcome the selective nature of gene panel testing and avoiding some of the problems implied by a „pure“ WES approach. While because of technical, interpretation-related and socio-ethical considerations, WES and especially whole-genome sequencing (WGS) still mostly remain to be used in a research setting, it is undoubtedly the genetic testing method of future clinical practice.

The use of chromosomal microarray in children with epilepsy – Estonian experience

Klari Noormets[1], Kadi Veri[2,3], Kadri Väljataga[4], Ulvi Vaher[1], Eve Õiglane-Shlik[1,2], Reet Rein[1], Aita Napa[1], Katrin Õunap[2,5], Tiia Reimand[2,5,6], Tiina Talvik[1,2], Inga Talvik[1,2] – [1]Children's Clinic of Tartu University Hospital, Tartu, Estonia; [2]Department of Pediatrics, University of Tartu, Tartu, Estonia; [3]Tallinn Children's Hospital, Tallinn, Estonia;[4]Internal Medicine Clinic of Tartu University Hospital, Tartu, Estonia; [5]Department of Genetics, United Laboratories of Tartu University Hospital, Tartu, Estonia; [6]Institute of Biomedicine and Translational Medicine; University of Tartu, Tartu, Estonia

BACKGROUND. Several chromosomal abnormalities have been described that can cause epilepsy and intractable epilepsy syndromes. Microarray-based genomic copy-number analysis (chromosomal microarray - CMA) gives a chance to detect very small chromosomal imbalances associated with different diseases.

AIM. Our aim was to evaluate the clinical use of CMA in a diagnostic process of children with epilepsy in our everyday practice and to find out how many patients with drug-resistant epilepsy in Estonia carry different CNV's.

METHODS. We examined all children who were diagnosed with epilepsy in 2009–2011 in Southern Estonia. All preformed CMAs and other investigations were recorded, in addition to general characteristics of the patients. Also we analysed the Estonian database of CMA analyses, which contains the data of 165 pediatric patients with epilepsy, analyzed in the same time period.

RESULTS. Of 174 children with newly diagnosed epilepsy CMA was performed in 30 (17.2%). Altogether 26.7% (8) of CMA showed some changes of which 7/8 could be related to epilepsy. Of the 174 newly diagnosed epilepsy patients 29 (16.7%) developed intractable epilepsy or epileptic encephalopathy. Of these 29 children, CMA was preformed at the first line in 14 (48.3%). From the Estonian CMA database we found altogether 46 CNVs in children with epilepsy (28%), of which 31 CNVs were found in patients diagnosed with refractory epilepsy (40% of patients with refractory epilepsy).

CONCLUSION. CMA is a useful diagnostic tool in detection of CNVs in epilepsy and it should be actively used in common clinical practice.

ACKNOWLEDGEMENTS. The study was supported by the EuroEPINOMICS grant SARLA11091E.

Targeted next generation sequencing as a diagnostic tool in 170 patients with epileptic encephalopathies

Rikke Steensbjerre Møller[1,2], Larsen LHG[3], Dahl HA[3], Olofsson K[1], Miranda M[4], Nielsen JEK[5], Lavard L[6], Linnet K[7], Uldall P[8], Tiina Talvik[9,10], Inga Talvik[9,10], Frangu M[11], Born PA[8], Gellert P[1], Nikanorova M[1,2], Jepsen B[1], Marjanovic D[1], Kragh-Olsen B[7], Brusgaard K[3], Hjalgrim H[1,2] – [1]Danish Epilepsy Centre, Dianalund, Denmark; [2]Institute for Regional Health Services, University of Southern Denmark, Odense, Denmark; [3]Amplexa Genetics, Odense, Denmark; [4]Department of Pediatrics, Herlev Hospital, Herlev, Denmark; [5]Department of Pediatrics, Roskilde Hospital, Roskilde, Denmark; [6]Department of Pediatrics, Hvidovre Hospital, Hvidovre, Denmark; [7]Department of Pediatrics, Aarhus University Hospital, Aarhus, Denmark; [8]Copenhagen University Hospital, Pediatric Clinic 1, Copenhagen, Denmark; [9]Department of Neurology and Neurorehabilitation, Children's Clinic of Tartu University Hospital, Tartu, Estonia; [10]Department of Pediatrics, University of Tartu, Tartu, Estonia; [11]Department of Pediatrics, Holbæk Hospital, Holbæk, Denmark

PURPOSE. Epilepsy is one of the most common neurological disorders, and is known to have a very heterogeneous background with a strong genetic contribution. In recent years several genes have been associated with epilepsy. However, making a genetic diagnosis in a patient can still be challenging as there is both genetic heterogeneity for a given epilepsy syndrome and phenotypic heterogeneity for a specific gene. The aim of this study was to develop a diagnostic screening method to analyze the genetic basis of childhood epilepsies.

METHOD. A gene panel targeting 45 known epilepsy genes was developed for next generation sequencing. Potentially causative variants were evaluated by literature and database searches and submitted to bioinformatic prediction algorithms. Variants were verified by Sanger sequencing and parents were included for segregation analysis. We used this panel on an unselected cohort of 170 patients, sequentially referred for panel testing. The majority of the patients had a range of epileptic encephalopathies or childhood epilepsies.

RESULTS. We identified a presumed disease-causing mutation in 41 of 170 patients. The aberrations encompassed known and unknown point mutations in several different genes e.g. *SCN1A, STXBP1, CDKL5, SCN2A, SCN8A, CHD2, GNAO1, GABRA1, GABRB3, KCNA2, STX1B*. All mutations were confirmed by conventional Sanger sequencing and, when possible, validated by parental testing and segregation analysis. A clinical follow-up

showed that the genetic diagnosis had led to changes in the medication in at least 15 of the patients.

CONCLUSION. We have developed a rapid and cost-efficient screening panel for the analysis of the genetic basis of childhood epilepsies. With this panel we were able to find a disease-causing genetic variation in 24% of the analyzed patients. Furthermore, this study demonstrates the potential for genetic diagnosis in epilepsy to influence treatment and to lead to specific, targeted treatment.

Epileptic encephalopathies – lessons learned

Inga Talvik[1,2], Rikke Steensbjerre Møller[3], Ulvi Vaher[1], Merilin Vaher[1], Klari Noormets[1], Stella Lilles[1], Margit Nõukas[4,7], Tiia Reimand[1,5,6], Anneli Kolk[1,2], Andres Metspalu[4,7], Tiina Talvik[1,2] – [1]Children's Clinic of Tartu University Hospital, Tartu, Estonia; [2]Department of Pediatrics, University of Tartu, Tartu, Estonia; [3]Danish Epilepsy Centre, Dianalund, Denmark; [4]Estonian Genome Foundation, Tartu, Estonia; [5]Department of Genetics, United Laboratories, Tartu University Hospital, Tartu, Estonia; [6]Institute of Biomedicine and Translational Medicine, University of Tartu, Tartu, Estonia; [7]Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia

Epileptic encephalopathies are a devastating group of severe childhood epilepsy disorders characterized by refractory, severe seizures and poor neurological outcome, in which the underlying causes often remain unknown. Making a genetic diagnosis in a patient can be challenging as there is both genetic heterogeneity for a given epilepsy syndrome and phenotypic heterogeneity for a specific gene. However, finding the underlying cause is important since it may lead to specific, targeted treatment. Using exome sequencing and targeted gene panels several genes have been associated with infantile epileptic encephalopathies.

Since 2013 we have had the possibility to use targeted gene panels for diagnosis of epileptic encephalopathies. During the past year 16 children were screened for 45 genes causing epileptic encepahlopathies. We identified a presumed disease-causing mutation in 6 of the 16 patients, corresponding to a hit ratio of 37.5%. The aberrations encompassed known and unknown point mutations in six different genes *CDKL5, SCN8A, GNAO1, GABRB3, ALG13* and *CPA6*. Furthermore, we found a likely disease causing mutation (*SCN1B* and *KCNT1*) in two more patients. Whole exome sequencing in patients with EE was used in 10 cases and following *de novo* mutations were found in 3 patients (*SCN8A, GRIA3; GABRB3)* for establishing the cause of epilepsy.

What we have learned is that clinical symptoms (phenotype) including EEG findings are changing during the disease course, that perinatal asphyxia/hypoxia can be part of EE symptoms and sometimes it is very difficult to say what the cause is and what the consequence is.

In conclusion, we would like to underline that gene panels and whole exome sequencing are powerful tools for finding the etiological diagnosis of epileptic encephalopathies.

The study was supported by the EuroEPINOMICS grant SARLA 11091E.

Four cases of *CDKL5*-related epileptic encephalopathy in Estonia: 1 female and 3 male patients

Stella Lilles[1], Inga Talvik[1,2], Klari Noormets[1,2], Ulvi Vaher[1], Katrin Õunap[2,3], Tiia Reimand[2,3,4], Valentin Sander[5], Pilvi Ilves[6,7], Tiina Talvik[1,2] – [1]Children's Clinic, Tartu University Hospital, Tartu, Estonia; [2]Department of Pediatrics, University of Tartu, Tartu, Estonia; [3]Department of Genetics, United Laboratories, Tartu University Hospital, Tartu, Estonia; [4]Institute of Biomedicine and Translational Medicine, University of Tartu, Tartu, Estonia; [5]Tallinn Children's Hospital, Tallinn, Estonia; [6]Radiology Clinic, Tartu University Hospital, Tartu, Estonia; [7]Department of Radiology, University of Tartu, Tartu, Estonia

INTRODUCTION. Cyclin-dependent kinase-like 5 (*CDKL5*)-related epileptic encephalopathy is a rare X-linked disorder caused by mutations in *CDKL5* gene characterized by intractable seizures and severe-to-profound developmental delay. *CDKL5*-related epileptic encephalopathy has mainly been detected in female patients and only 22 boys have been reported so far according to our best knowledge. In most of the cases the phenotype in boys is more severe, consisting of early-onset intractable epilepsy, severe global developmental delay, hypotonia and cortical visual impairment. The purpose of the presentation is to report the first cases of *CDKL5*-related epileptic encephalopathy in three male patients and in one female patient diagnosed in Estonia.

PATIENTS. We report the main clinical, radiologic and neurophysiologic findings in comparison of the genotypes of the studied four patients. We identified a novel *de novo* heterozygous frameshift mutation in exon 15 of the *CDKL5* gene in one male, a previously reported *de novo* hemizygous missense mutation in exon 14 in two male patients, and a *de novo* heterozygous frameshift mutation in exon 12 in a girl. Our study shows that the phenotype of our male patients is more severe than that of the female patient, characterized by earlier onset of epileptic encephalopathy, more severe developmental delay and brain atrophy in contrast to our female patient. The studied patients share similar clinical characteristics with previously reported patients with *CDKL5* mutations.

CONCLUSION. It is important to use an epilepsy gene panel as the first-line tool for investigation in cases with a very early onset of seizures and suspicion of early infantile epileptic encephalopathy (EIEE).

The study was supported by the EuroEPINOMICS grant SARLA11091E.

STROKE IN CHILDREN

Neuroimaging in pediatric stroke: Diagnosis, prognosis, and plastic recovery

Adam Kirton – Calgary Pediatric Stroke Program, Alberta Children's Hospital Research Institute, Departments of Pediatrics and Clinical Neurosciences, University of Calgary, Calgary, Canada

Modern neuroimaging has revolutionized our understanding of stroke in the fetus, newborn, and child. Diagnostically, imaging applications can differentiate specific stroke diseases across ischemic and hemorrhagic conditions, arterial versus venous localizations, and suggest discrete pathophysiological mechanisms with immediate implications for treatment. Prognostically, imaging biomarkers are increasingly defined that can aid in early decision making, secondary stroke prevention strategies, and counseling of families. Advanced neuroimaging modalities including task and resting state functional MRI and diffusion imaging are integrating with other neurotechnologies such as transcranial magnetic stimulation to inform new models of plastic brain reorganization following stroke in children. Novel therapies have resulted where the same imaging tools may be able to assess the mechanisms of intervention-induced change in the developing brain.

Epilepsy after perinatal stroke

Rael Laugesaar[1,2], Pilvi Ilves[3,4], Ulvi Vaher[2], Silva Lõo[1,5], Anneli Kolk[1,2], Dagmar Loorits[4], Tiiu Tomberg[4], Inga Talvik[1,2], Valentin Sander[6], Tiina Talvik[1,2] – [1]Department of Pediatrics, University of Tartu, Tartu, Estonia; [2]Children's Clinic of Tartu University Hospital, Tartu, Estonia; [3]Department of Radiology, University of Tartu, Tartu, Estonia; [4]Radiology Clinic of Tartu University Hospital, Tartu, Estonia; [5]Department of Pediatric Neurology, Helsinki University Hospital, Helsinki, Finland; [6]Tallinn Children's Hospital, Tallinn, Estonia

INTRODUCTION. The aim of the study was to find out the prevalence and predictive factors of epilepsy after perinatal stroke.

METHODS. Patients were recruited from the Estonian Paediatric Stoke Registry in March, 2015. The study group consisted of 77 children with perinatal stroke (38 boys, 39 girls). Neuroimaging studies were reviewed by neuroradiologists and were classified according to the vascular type. Three children (4%) had antenatal stroke, 33 (43%) had neonatal stroke (arterial ischemic stroke in 18, intracerebral haemorrhage in 4, sinovenous thrombosis in 3, and periventricular venous hemorrhagic infarction in 8 cases), and 41 (53%) had presumed perinatal stroke (periventricular venous infarction in 28 and arterial stroke in 13 cases). The left hemisphere was the prominent side in 53 cases (70%). Mean follow-up time was 8.3 years (range: 1 month to 20 years).

RESULTS. Twenty-five (32%) children developed epilepsy. Median onset of epilepsy was 4.1 years (range 1 month to 18 years). The Kaplan-Meier probability of remaining seizure-free at 4 years was 82.6%. Epilepsy occurred more often in children with neonatal stroke than in children with presumed perinatal stroke (44% and 22%, $P = 0.04$). Arterial stroke was significantly more often associated with epilepsy compared to periventricular venous infarction (49% and 19%, $P < 0.01$). The side of the damage was not associated with onset of epilepsy ($P = 0.41$). Neonatal seizures did not predict later epilepsy in children with neonatal stroke ($P = 0.50$).

CONCLUSIONS. Epilepsy occurs in 32% of children with perinatal stroke. Improved knowledge of epilepsy predictors after perinatal stroke allows to more adequately counsel families with children with perinatal stroke.

This study was supported by the Estonian Research Council grant PUT (148).

A retrospective study: cerebral ischemic stroke in children and young people at the Children's Clinical University Hospital (Riga, Latvia)

Mikus Jakovickis – Neurology and Neurosurgery Clinic, Children`s Clinical University Hospital, Riga, Latvia

OBJECTIVE. The aim of the research was thorough retrospective study of the diagnosis and therapy of acute ischemic stroke (AIS), transient ischemic attack (TIL) and venous sinus thrombosis (VST), to find out epidemiological indicators and risk factors for patients aged 28 days to 18 years, who were treated in Riga Children`s Clinical University Hospital from January 2003 to May 2014.

METHOD. Within the research Riga Children Clinical University Hospital archive`s patient cards ICD 10 I60 – I69 were selected and analysed. Cards of the patients who were treated from January 2003 to May 2014 were selected.

RESULTS. 26 patients were selected (incidence 0.55 / 100 000), of these 20 were AIS, 4 were TIA, 2 were SVT. There were more boys than girls (15 boys, 11 girls) in the study group. The average age of the patients was 8 years.

Ten patients (38.5%) had at least one risk factor. Five patients (19.2%) had cardiac risk factors, 3 patients (11.5%) had prothrombotic factors. Maternal risk factors were not recorded for any patient. In four cases acute neurologic deficit was observed 24 hours after a mild head or neck trauma. Two cases with SVT risk factors were not clear. All patients underwent radiological diagnostic. Thirteen patients received antiplatelet therapy, 8 received anticoagulants, 3 received corticosteroids and 13 received the nootropic medicine. Twelve (46%) patients were discharged from the hospital with a neurological defect, 2 (7.8%) died during hospitalization.

CONCLUSIONS. The overall incidence of ischemic stroke was 0.55 / 100 000, but the data do not reflect the current overall statistics for Latvia. The observed symptoms were motor and sensor deficit and aphasia; cramps and headaches occurred less frequently compared with relevanr literature data. The most common risk factors were heart abnormalities, artheriopathies, head or neck injuries, prothrombotic state. Ten patients (38.5%) had at least one risk factor, five (19.2%) had more than one factor. The incidence was higher for boys than for girls.

Risk factors, clinical and radiological findings in presumed perinatal stroke

Pilvi Ilves[1,2], Rael Laugesaar[3,4], Dagmar Loorits[1], Anneli Kolk[3,4], Tiiu Tomberg[1], Silva Lõo[3], Inga Talvik[3,4], Tiina Kahre[3,5], Tiina Talvik[3,4] – [1]Radiology Clinic of Tartu University Hospital, Tartu, Estonia; [2]Department of Radiology, University of Tartu, Tartu, Estonia; [3]Department of Pediatrics, University of Tartu, Tartu, Estonia; [4]Children's Clinic of Tartu University Hospital, Tartu, Estonia; [5]Department of Genetics, United Laboratories of Tartu University Hospital, Tartu, Estonia

BACKGROUND AND PURPOSE. It is unknown why some infants with perinatal stroke present clinical symptoms late during infancy and will be identified as infants with presumed perinatal stroke.

METHODS. The risk factors and clinical data of 44 infants with presumed perinatal stroke from the Estonian Pediatric Stroke Database were retrospectively reviewed. All radiological images from the Estonian Digital Picture Archiving System and from two tertiary hospital archives were retrospectively reviewed by three neuroradiologists blinded to the clinical findings. According to the vascular syndrome, ischemic insult was classified as arterial ischemic stroke or periventricular venous infarction.

RESULTS. Children with presumed perinatal stroke were in 90% of cases born at term, in 43% of cases without risk factors during pregnancy or delivery and in 22% of cases prothrombotic changes were the only risk factor. Among children with presumed perinatal stroke, periventricular venous infarction was identified in 59% and arterial ischemic stroke in 41% of children. Children with periventricular venous stroke were born significantly more often ($p < 0.05$) vaginally (82%) compared to arterial stroke infants (43%) and were all symptom free after birth. The infants with arterial ischemic stroke had statistically more often acute perinatal risk factors as meconial stained liquid ($p < 0.01$), need for resuscitation ($p < 0.001$) and lower 1 minute Apgar score ($p < 0.05$) compared with the infants with periventricular venous infarction.

CONCLUSIONS. Infants with presumed perinatal stroke had periventricular venous infarction in two thirds of the cases and were born at term with no symptoms after birth, the disease being probably of prenatal origin.

This study was supported by the Estonian Research Council grant PUT (148).

Neurodevelopmental outcome after neonatal and presumed perinatal stroke at preschool to early school age

Silva Lõo[1,2], Mairi Männamaa[3,4], Rael Laugesaar[2,4], Pilvi Ilves[5,6], Dagmar Loorits[5], Tiiu Tomberg[5], Anneli Kolk[2,4], Inga Talvik[2,4], Tiina Talvik[2,4], Leena Haataja[7]– [1]Department of Pediatric Neurology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [2]Department of Pediatrics, University of Tartu, Tartu, Estonia; [3]Institute of Psychology, University of Tallinn, Tallinn, Estonia; [4]Children's Clinic of Tartu University Hospital, Tartu, Estonia; [5]Radiology Clinic of Tartu University Hospital, Tartu, Estonia; [6]Department of Radiology, University of Tartu, Tartu, Estonia; [7]Department of Child Neurology, Turku University Hospital, Turku, Finland

BACKGROUND AND PURPOSE. Perinatal stroke is an acknowledged cause of life-long neurological morbidity, however, its long-term neurodevelopmental outcomes are unclear. The purpose of the study was to evaluate neurological and cognitive outcomes following neonatal stroke (NS) and presumed perinatal stroke (PPS) at preschool to early school age.

METHODS. Forty-three term-born children with perinatal stroke (16 NS, 27 PPS, age 3–12 years) were enrolled from Estonian Paediatric Stroke Database. Pediatric Stroke Outcome Measure (PSOM) and Kaufman Assessment Battery for Children – Second Edition (K-ABC-II) were used as the outcome measures. Laterality, vascular origin and extent of stroke were defined.

RESULTS. At a median age of 7.6 years, 81% of NS and 89% of PPS showed poor neurodevelopmental outcome (mean total PSOM score 2.7 and 2.0, respectively). While moderate to severe hemiparesis prevailed in the PPS subgroup (81% in PPS, 50% in NS; $P = 0.04$), language impairments were significantly more common after NS (50% in NS, 11% in PPS; $P = 0.01$). Both subgroups showed significantly lower cognitive ability in comparison to age equivalent K-ABC-II normative mean. Large stroke size was associated with poorer overall outcome and weaker cognitive performance in both subgroups, and predicted degree of motor impairment in children with NS. Moderate to severe language impairments were only seen among children with left-sided strokes. Left hemisphere strokes were predominant in both subgroups. The most common lesion type was middle cerebral artery stroke in the NS and periventricular venous infarction in the PPS subgroup.

This study was supported by the Estonian Research Council grant PUT (148).

CONCLUSIONS. All children with perinatal stroke are at risk for emerging neurodevelopmental deficits irrespective of the subtype of stroke or level of motor impairment, and require long-term neurodevelopmental follow-up.

This study was supported by the Estonian Research Council grant PUT (148).

Ophthalmoplegic migraine in childhood: case report

Jūratė Laurynaitienė[1], Nerija Vaičienė-Magistris[1], Rymantė Gleiznienė[2] – [1]Department of Neurology, Lithuanian University of Health Sciences, Kaunas, Lithuania; [2]Department of Radiology, Lithuanian University of Health Sciences, Kaunas, Lithuania

INTRODUCTION. Ophthalmoplegic migraine (OM) is a rare episodic childhood condition characterized by recurrent episodes of headache with unilateral ophthalmoplegia due to paresis or paralysis of the 3rd, 4th or 6th cranial nerves. The disease is reversible and is thought to be self-limited. There is suggestion that the findings of magnetic resonance imaging (MRI) should serve as the hallmarks of OM in children.

CASE REPORT. We report a six-year-old boy with previously normal development who started to experience repeated episodes of unilateral right ptosis and headache since the age of 1 year 3 months. The first episode lasted for a few weeks and resolved spontaneously. At that time brain CT was normal and neuroboreliosis was excluded. One year later the second episode of the right ptosis occurred following fever and resolved spontaneously in a few days as well. The third attack occurred at the age of 3 years and presented with ptosis followed by headache lasting for three days. Ptosis resolved spontaneously, however, headache was abolished only by administration of acetazolamide. Brain MRI performed during remission was normal although repeated MRI at the age of 4 years and 7 months during the fourth episode of continued headache with vomiting and diplopia displayed changes in the proximal part of the 3rd nerve. In the past year the patient was free from OM episodes.

CONCLUSION. Diagnosis of ophthalmoplegic migraine should be supported by findings on MRI performed during or immediately after migraine-like headache demonstrating enlargement of the 3rd nerve at the root entry zone.

Incidence of childhood epilepsy in Estonia

Kadi Veri [1,2], Inga Talvik [1,3], Oivi Uibo [1,3], Aita Napa[3], Ulvi Vaher[3], Eve Õiglane-Shlik[1,3], Anneli Kolk[1,3], Reet Rein[3], Tiina Talvik [1,3] – [1]Department of Pediatrics, University of Tartu, Estonia; [2]Tallinn Children`s Hospital, Estonia; [3]Children`s Clinic, Tartu University Hospital, Estonia

PURPOSE. The aim of the study was to establish the incidence rate (IR) of childhood epilepsy in Estonia and to describe the structure of childhood epilepsy.

STUDY GROUP. This study is a population-based prospective epidemiological study carried out from January 1, 2009 to December 31, 2011 in southern Estonia. All patients (aged 1 month to 19 years) with newly diagnosed epilepsy were included. Patients with neonatal and febrile seizures were excluded; 180 children met the study criteria (96 males and 84 females).

RESULTS. The total IR of childhood epilepsy was 80.0 / 100 000. The IR was the highest (147.8 / 100 000) in the age group 5 to 9 years; and the second highest in the age group 1 month to 4 years (101.2 / 100 000). Mean age at seizure onset was 7.8 years. Generalized seizures occurred in 25.0% and focal seizures in 54.4% of epilepsy patients. According to the new ILAE proposed classification (ILAE 2010), specific electroclinical syndromes were identified in 23.9% of cases, structural or metabolic etiology in 18.3% of cases and presumed genetic origin in 5.5% of cases. In 52.2% of cases, the cause of epilepsy remained unknown. A family history of epilepsy was recorded in 13% of cases. Whole-genome genotyping was performed in 32 patients. We identified 8 copy number variants (CNVs), including 6 deletions and 2 duplications.

CONCLUSION. IR of childhood epilepsy in the present study (80.0 / 100 000) was approximately twice higher compared with that found in the first epidemiological study of childhood epilepsy in Estonia (45 / 100 000, Beilmann et al 1999), which can be explained by better case collection and improved diagnostic possibilities.

This study was supported by the Estonian Research Council grant PUT (148).

Antiepileptic drugs used in the treatment of European neonates contain potentially harmful excipients - analysis of the ESNEE point prevalence study

Anu Bärenson[1], Georgi Nellis[1,2], Heili Varendi[1,2], Tuuli Metsvaht[1,2], Irja Lutsar [2] on behalf of ESNEE project – [1]Tartu University Hospital, Tartu, Estonia; [2]University of Tartu, Tartu, Estonia

Pharmaceutical excipients used in medicines to facilitate manufacture and storage can be potentially harmful. Excipients associated with adverse effects in neonates (excipients of interest; EOI) include parabens, saccharin sodium, benzalkonium chloride, benzoates, ethanol, propylene glycol, polysorbate 80 and sorbitol.

We aimed to evaluate the exposure of neonates to EOI through antiepileptic drugs (AEDs) in European NICUs and to explore the availability of excipient-free products for substitution.

Methods: The Europe-wide point prevalence study of the European Study of Neonatal Excipient Exposure (ESNEE) project recorded all medicines prescribed to neonates within one day in 2012. All AED prescriptions registered in the study were included in the analysis.

Results: Eighty-nine neonatal units from 21 European countries joined the ESNEE project. Altogether 726 neonates, 2095 prescriptions and 530 products were registered. AED were prescribed to 19 neonates in 31 occasions (1.5% of all prescriptions) involving 23 (4.3%) products. The AEDs included phenobarbital, midazolam, lorazepam, diazepam, clonazepam, clobazam, levetiracetam, phenytoin and valproic acid. One or more EOI were found in 9 (39%) products prescribed to 12 (63%) neonates. The most widely used AED was phenobarbital with 17 (55%) prescriptions for 9 products. Propylene glycol was the most frequent EOI found in 7 products (78%). Four of these were parenteral phenobarbital formulations, for which a EOI-free substitution was available in the European market.

Conclusion: Overall exposure to EOI through AED is low due to infrequent use of these drugs in neonates. However, a high proportion of AEDs contains EOI, especially propylene glycol, associated with serious toxicity in neonates. Substitution with EOI-free alternatives of the same active ingredient and route of administration would allow reduction in unnecessary exposure.

Findings of neuroimaging in children with developmental disabilities

Jurgita Grikiniene, Monika Vincerauskaite – Vilnius University, Faculty of Medicine, Clinic of Children's Diseases, Vilnius, Lithuania; Children's Hospital, affiliate of Vilnius University Hospital Santariškių Klinikos, Paediatrics Centre, Vilnius, Lithuania

PURPOSE. To analyse the findings of neuroimaging in children with development disabilities.

METHODS. Retrospective analysis was performed at the Department of Child Neurology, Children's Hospital, affiliate of Vilnius University Hospital Santariškių klinikos in 2013. We analysed 309 cases: 130 (42%) girls and 179 (58%) boys.

RESULTS. Neuroimaging investigations were performed in 239/309 (77%) patients: only CT was performed in 5/239 (23%) patients, only MRI was performed in138/239 (58%) patients, and CT and MRI were performed in 46/239 (19%) patients. Pathological changes were found in 143/239 (60%) patients.

Cerebral palsy (CP) occurred in 113/309 (37%) patients. Neuroimaging was performed in 95/113 (84%) patients. Changes were found in 67/95 (71%) patients (32/65 (49%) in CT, 43/63 (68%) in MRI).

Spastic hemiplegic CP occurred in 24/113 (21%CP) patients. Neuroimaging was performed in 18/24 (75%) patients. Changes were noted in 17/18 (94%) patients.

Spastic quadriplegic CP occurred in 29/113 (26%CP) patients. Neuroimaging was performed in 26/29 (90%) patients. Changes were observed in 20/26 (77%) patients.

Spastic diplegic CP occurred in 27/113 (24%CP) patients. Neuroimaging was performed in 25/27 (93%) patients. Changes were recorded in 15/25 (60%) patients.

Dyskinetic CP occurred in 7/113 (6%CP) patients. Neuroimaging was performed in 4/7 (57%) patients. Changes were recorded in 3/4 (75%) patients.

Ataxic CP occurred in 18/113 (16%CP) patients. Neuroimaging was performed for 16/18 (89%). Changes were in 8/16 (50%).

Mixed CP was in 8/113 (7%CP). Neuroimaging was performed in 6/8 (75%) patients. Changes were noted in 3/6 (50%) patients.

Autism occurred in 23/309 (7%) patients. Neuroimaging was performed in 18/23(78%) patients. Changes were recorded in 6/18 (33%) patients.

Mental retardation occurred in 38/309 (12%) patients. Neuroimaging was performed in 26/38 (68%) patients. Changes were recorded in 13/26 (50%) patients.

Specific mixed developmental disorder occurred in 120/309 (39%) patients. Neuroimaging was performed in 90/120 (75%) patients. Changes were detected in 52/90 (58%) patients.

Specific motor developmental disorder occurred in 15/309 (5%) patients. Neuroimaging was performed in 10/15 (67%) patients. Changes were noted in 5/10 (50%) patients.

CONCLUSIONS. The most common development disorders were specific mixed developmental disorder at 39% and cerebral palsy at 37%.

Neuroimaging investigations were performed in 77% of the patients and pathological changes were found in 60% of the patients.

Most of the changes were found in the case of CP, 71% (in the case of spastic hemiplegic CP, 94%), and least of the changes were found in the case of autism, 33%.

Tammistu Family Centre – a competence centre for families of children with rare disorders

Tiina Stelmach, Tiina Talvik – Estonian Agrenska Foundation, Tartu University Hospital, Children's Clinic, Tartu, Estonia

The Estonian Agrenska Foundation was established in 2003. There are currently over 7000 children with disabilities in Estonia, with ~ 4000 children with severe and profound disabilities.

The aim was to set up Tammistu Family Centre as a competence centre for development and implementation of services for children with special needs and their families, with special attention to persons with rare disorders.

The mission of Tammistu Family Centre is:

To create regular supportive services for better future for children with rare disorders, as well as with other disabilities with complex needs.

To relieve the burden of families, whose children are totally dependent on caregivers.

To provide and develop possibilities for job exercises and sheltered work for adults with intellectual and complex disabilities.

To support optimal independence for young adults within their potential to enter the labour market.

Network of services:

1. Respite care since 2006 for children with severe disabilities:
   a. Enables the parents to maintain and lead their professional life more normally
   b. Grants them some time for recreation
   c. Teaching of social skills to children and youths with disabilities in order to be more independent
2. Disability-specific family programmes:
   Training and information dissemination on:
   1. Essence of a certain disorder
   2. Coping strategies & early intervention
   3. Supportive services & legislation
   4. Parent-to-parent support
3. Supported employment unit – activities since 2007:
   Practical work in the park (gardening) of Tammistu – for people with intellectual disabilities.
4. Advanced education for parents, professionals and other network members.
5. Practical base for students of the University of Tartu (medicine, physiotherapy, social work, etc) for work with persons with special needs.

Tuberous sclerosis complex and epilepsy: ten years of experience

Dovilė Jonuškaitė[1,3], Rūta Samaitienė[2,4], Rūta Praninskienė[2,4], Rimantė Čerkauskienė, PhD, MD[3,4] – [1]Vilnius University Faculty of Medicine; [2]Children's Hospital, Affiliate of Vilnius University Hospital Santariskiu Klinikos, Children's Neurology Department; [3]Children's Hospital, Affiliate of Vilnius University Hospital Santariskiu Klinikos, Coordinating Centre for Rare Paediatric Diseases; [4]Vilniaus Universitetas, Medicinos fakultetas, Vaikų ligų klinika (Vilnius University Faculty of Medicine, Clinic of Children's Diseases

OBJECTIVE. a) To describe a single center experience in the diagnosis and treatment of paediatric tuberous sclerosis complex patients. b) To present a complex case of intractable epilepsy related to brain tuber.

MATERIAL AND METHODS. Tuberous sclerosis complex was diagnosed in 22 patients. Genotype: one patient *TSC2* mutation positive, two patients *TSC1* mutation positive. In two patients neither of these two mutations were found. In 87% cases epileptic seizure was the first documented symptom. At least one seizure was reported in all patients who were followed up for a convenient time (21 cases), the diagnosis of epilepsy was confirmed in all of them. Of patients' seizures 14% were generalized. 67% of patients reported focal seizures, in 43% of the cases it was the first seizure type with manifestation at the median age of 2 years (min. 3 months, max. 9 years). In 43% of the cases patients suffered from epileptic spasms, in all cases it was the first type of attack. The median age at the onset of spasms was 6 months (min. 4, max 12). Subependymal giant cell astrocytoma was diagnosed in a single case.

A case of intractable epilepsy is presented to elucidate difficulties of seizure management in complicated cases of tuberous sclerosis complex.

CONCLUSIONS. Compared with data from other publications, a greater proportion of patients had epilepsy, but the difference was not statistically significant.

CLINICAL NEUROPSYCHOLOGY AND NEUROREHABILITATION IN CHILDREN

The impact of epilepsy on social competence and cognitive function in 7-12- year-old children

Triin Raud[1,2], Marianne Saard[1,3], Mari-Liis Kaldoja[1], Anneli Kolk[1,3] – [1]University of Tartu, Department of Psychology, Tartu, Estonia; [2]Randvere School, Tallinn, Estonia; [3]Children's Clinic of Tartu University Hospital, Tartu, Estonia

INTRODUCTION AND AIM. Neurocognitive and social dysfunction are reported in children with epilepsy. An essential component of social competence is the Theory of Mind (ToM) – the ability to understand the mental state of others. The purpose of the study was to explore the influence of epilepsy on social competence and neurocognitive development.

METHOD. A total of 35 children with epilepsy (M = 10.46 yrs; SD = 1.85): 10 with partial and 25 with generalized epilepsy and 30 controls (M = 10.26 yrs.; SD = 1.88) participated in the study. Mean onset of epilepsy was 9.1 yrs (SD = 2.08). Social competence was evaluated using ToM stories and the Social Cognition Questionnaire. Neurocognitive development was assessed using NEPSY battery. The results were analysed with SPSS Statistics 20.

RESULTS. Specific assessment showed significantly lower social cognition in children with epilepsy compared to healthy peers. As was the case with the healthy children, the epilepsy group understood false belief stories better than intentional lying and sarcasm ($p < .05$). Scores for intentional lying tests were higher than for the sarcasm test ($p < .05$), although all of the previous skills were delayed in development. The cognitive findings in the epilepsy group showed specific deficit in attention, and in executive, verbal and fine motor skills ($p < .05$). Children with early epilepsy onset (before 9.1 years) had lower scores for intentional lying ($p < .05$). Lower social skills ($p < .05$) were also confirmed by parents' ratings. Remarkably, children with partial epilepsy outperformed children with generalized epilepsy in sarcasm ($p < .05$) and memory function ($p < .05$).

CONCLUSION. Children with epilepsy showed lower functioning in social and overall neurocognitive performance. Especially vulnerable are children with early onset and generalized epilepsy. The results indicate the importance of assessment of social and cognitive functions in everyday clinical practice. Special attention should be paid on the type of epilepsy.

Generalized effect of cognitive neurorehabilitation in children with epilepsy based on parental feedback

Anneli Kolk[1,2], Agne Põlder[3], Carmen-Kristiina Parik[4], Madis Bachmann[3], Lisanna Pertens[3], Marianne Saard[2,3] – [1]Department of Pediatrics, Faculty of Medicine, University of Tartu, Estonia; [2]Department of Neurology and Neurorehabilitation, Children's Clinic, Tartu University Hospital, Estonia; [3]Department of Psychology, University of Tartu, Estonia; [4]Department of Public Health and Faculty of Medicine, University of Tartu, Estonia

OBJECTIVE. Partial epilepsy (PE) in children is often accompanied by attention and visuospatial impairments. There exist few neurorehabilitation techniques and outcome measures for children. Our aim was to measure the effectiveness of cognitive neurorehabilitation for every-day life, namely the generalized effect, using parental feedback and children's evaluation as a method complementary to objective measures.

METHODS. Sixteen PE children (mean age = 10.07 yrs, SD = 1.149) with cognitive impairment attended individual attention and visuospatial training using the FORAMENRehab software (Sarajuuri et al., 2000*). Trainings occurred twice a week during a 5-week-period. Eleven PE children in the waiting-list group (mean age = 10.51 yrs, SD = 1.766) participated in baseline assessments with no training. The generalized effect was evaluated by parents' and children's questionnaires on perceived attention, behaviour and school performance before and 1.36 years (SD = 0.391) after intervention, in addition to objective baseline assessments during long-term follow-up.

RESULTS. Parents' feedback showed positive behavioural change: the children were less distracted and more prone to social communication. Skills in reading, writing, mathematics, visuomotor functions improved. The children stated improved concentration skills and functioning in school tasks. During follow-up, the baseline assessments study group showed sustained significant improvements in attention functions: *focused attention, complex attention, tracking* ($p < 0.05$); and visuospatial functions: *visual recognition, visual organization, visual attention, visuospatial perception* ($p < 0.05$). The waiting-list group only performed better in one *complex attention* task and in some aspects of visuospatial tasks ($p < 0.05$).

CONCLUSION. Sustained positive rehabilitation effect based on objective measures was confirmed by parents as a marked positive change in every-day life situations. The generalized effect of rehabilitation was manifested in children's behaviour and overall performance in school. The children reported preference of visuospatial perception tasks: *maze* and *pattern construction*, hence attention training requires more motivation. The results confirmed the effectiveness of the FORAMENRehab rehabilitation design.

Personalized approach and importance of individual differences in pediatric neurorehabilitation

Marianne Saard[1,2], Agne Põlder[1], Carmen-Kristiina Parik[3], Madis Bachmann[1], Lisanna Pertens[1], Anneli Kolk[2,4] – [1]Department of Psychology, University of Tartu, Estonia; [2]Department of Neurology and Neurorehabilitation, Children's Clinic, Tartu University Hospital, Estonia; [3]Department of Public Health, Faculty of Medicine, University of Tartu, Estonia; [4]Department of Pediatrics, Faculty of Medicine, University of Tartu, Estonia

OBJECTIVE. Children with partial epilepsy (PE) often show cognitive deficits. Using modern and attractive neurorehabilitation methods is crucial in remediation. Our aim was to investigate the effectiveness of personalized intervention in individual cognitive improvement in children with PE.

METHODS. Children with PE: 16 in the study group (mean age = 10.07 yrs, SD = 1.149), 11 in the waiting-list group (mean age = 10.51yrs, SD = 1.766) and 19 healthy age-matched controls participated in baseline assessments. Thereafter, the study group passed attention and visuospatial rehabilitation during 5 weeks (10 sessions) with computer-based FORAMENRehab (Sarajuuri et al, 2000; adapted for children by the authors). Three or 4 difficulty levels were developed for 9 attention and 11 visuospatial tasks to measure individual progress. The results were analysed with Mann-Whitney-Wilcoxon and Wilcoxon signed-rank tests.

RESULTS. At baseline, all patients performed significantly worse compared to healthy children in various attention and visuospatial functions ($p < 0.05$). After training, significant improvement was seen for the study group in the following attention functions: *complex attention* ($p < 0.05$), *tracking* ($p < 0.01$); and in visuospatial functions: *visual organization, visual attention*, *visuospatial perception* ($p < 0.05$). The waiting-list group only performed better in one aspect of *visuospatial perception* ($p < 0.05$). A slower rehabilitation effect was seen in *complex attention* and *tracking*: children's average attained level was 1.75 of maximal 4 and 1.31/3, respectively; in *visual recognition:* 1.85/4 and *visuospatial perception*: 1.94/4. After intervention, children with better progress had reached approximately 1.5–2 times higher difficulty levels. Individual scores for attention and visuospatial tasks were well correlated (Pearson´s $r = 0.61$).

CONCLUSION. Neurorehabilitation with FORAMENRehab is effective for children with PE. Efficient methods should focus on specific components of impaired functions. Individual approach with consideration of each child's progress is an important basis for remediation as some children require longer training.

Advances in pediatric stroke rehabilitation: Non-invasive brain stimulation

Adam Kirton – Calgary Pediatric Stroke Program, Alberta Children's Hospital Research Institute, Departments of Pediatrics and Clinical Neurosciences, University of Calgary, Calgary, Canada

As a focal injury of defined timing in an otherwise healthy brain, perinatal stroke represents an ideal human model of developmental plasticity. Animal studies have combined with human evidence using advanced neuroimaging and transcranial magnetic stimulation (TMS) neurophysiology to create working models of how brain functions organize themselves during development. These models have identified central targets for neuromodulation with translation into clinical trials of rTMS and transcranial direct current stimulation (tDCS). Modulation of the motor system to enhance function in hemiparetic children is the primary example but extrapolation to other stroke-related morbidities will be discussed. Emerging technologies and future directions will be considered.

NEONATAL NEUROLOGY

HIE - impact of asphyxia and reoxygenation

Ola Didrik Saugstad – Department of Pediatric Research, University of Oslo, Oslo, Norway

Worldwide 800 000 newborns die and 250–750 000 newborns develop encephalopathy following intrapartum related events. Of these a substantial number develop long term impairment as cognitive deficiency, cerebral palsy, epilepsy or sensory defects.

Recent data indicate that the number and severity of encephalopathy following intrapartum related events are aggravated by exposure to hyperoxia. Studies in newborn rodents and piglets demonstrate that pure oxygen has a dramatic detrimental effect on the brain.

Klinger et al. showed in 2005 that one or more hyperoxic episodes in the first 2 h of life resulted in a significantly worse outcome at 18 months of follow up. If hyperoxia was combined with hypocapnia, the outcome became even worse, giving a 4-fold greater odds ratio for an impaired outcome at the age of 18 months.

A meta-analysis by Saugstad et al (2012) was performed of 3 studies of newborn infants resuscitated at birth with air or pure oxygen. A total of 414 children were evaluated (73% of eligible children; 195 resuscitated with air and 219 with 100% oxygen). In the air group, 12.8% of infants had an abnormal neurodevelopmental outcome, compared with 10.5% in the 100% oxygen group [typical relative risk (RR) 1.24, 95% confidence interval 0.73–2.10].

Another meta-analysis of ten studies (Saugstad et al, 2012) found that there were 150 of 1,082 (13.9%) infants in the 21% oxygen group that had HIE stage 2 or 3 compared to 172 of 1,051 (16.4%) infants in the 100% oxygen group (typical RR 0.88, 95% CI 0.72, 1.08). In subgroup analysis of the 6 truly randomized studies, 38 out of 449 (8.5%) infants in the room air group and 40 out of 387 (10.3%) infants in the 100% O 2 group developed HIE stage 2 or 3 (typical RR 0.89, 95% CI 0.59, 1.34). Khapadia et al (2013) published data showing in term babies with birth asphyxia a strong association between a high paO_2 at admission to the NICU and moderate to severe encephalopathy.

It therefore seems that hyperoxia aggravates the injury after an intrapartum related asphyxia/hypoxia. These finding have implications for clinical handling of asphyxic newborn infants. Keep oxygenation as "normal" as possible both during and after the resuscitation period. This may reduce brain injury and the need for hypothermia.

Outcome for 2-year-olds born at very low gestational age in Estonia: are there any improvements?

Heili Varendi[2,3], Svetlana Müürsepp[1], Hele Rüga[2,3], Liis Toome[1,3] – [1]Tallinn Children's Hospital, Tallinn, Estonia; [2]Children's Clinic of Tartu University Hospital, Tartu, Estonia; [3]University of Tartu, Tartu, Estonia

Survival of very low gestational age (VLGA; 22^{+} to 31^{+6} weeks of gestation) infants until discharge from hospital in Estonia has increased from 78% in 2002–2003 to 85% in 2007–2008 and 92% in 2011–2012. Increased survival concerns higher impairment rates. Two years of corrected age (2yCA) is considered an acceptable time for assessment high-risk (incl VLGA) infants for long-term morbidities.

The aim was to evaluate outcome of the Estonian national one-year (2011–2012) VLGA cohort at 2yCA and compare it with that of an earlier (2007) cohort.

METHODS. A national population-based cohort of Estonian VLGA infants born between 01.05.2011 and 30.04.2012 was studied prospectively within the EPICE (Effective Perinatal Intensive Care in Europe) project. The parents of the infants who had survived at 2yCA were asked to fill in adapted PARCA-questionnaire with subsections about child developmental skills, health and diseases. Questions describing infants' treatment needs, vision, hearing, and ability to walk, sit and understand instructions, as well as the number of words the infant could say were selected for analysis of the neurodevelopmental status.

RESULTS. Of 139 survived infants, data were obtained for 138. There were no children with blindness, hearing loss or on seizure medications. All children were able to say words (median 53 (range 2–100)). Eight infants (5.8%) were unable to walk without assistance or aids, of them 4 were unable to sit without support (Gross Motor Function Classification System, levels 3–5).

In comparison with 2007, in 2011–2012 the survival of all liveborn VLGA infants at 2yCA without severe impairment of motor development increased from 76% to 86% ($p < 0.05$).

CONCLUSION. Outcome for liveborn VLGA infants at 2yCA has improved in Estonia, at least according to parental reports.

Gender differences in developmental outcomes of Estonian preterm children at the age of two and five years and the relationships between the outcomes

Mairi Männamaa[1,2], Heili Varendi[1], Liis Toome[3] – [1]Children's Clinic of Tartu University Clinics, Tartu, Estonia; [2]Institute of Psychology, University of Tallinn, Tallinn, Estonia; [3]Clinic of Paediatrics, Tallinn Children`s Hospital, Tallinn, Estonia

BACKGROUND AND PURPOSE. Advances in perinatal care have improved the survival of preterm (PT) infants. Still, the risk of impairments remains high in several areas of development. Early developmental outcomes do not always lead to poor outcomes in the future. The purpose of the study was to evaluate the developmental outcomes and gender differences in PT children at the age of two and five years and to compare the results with the results for full-term (FT) controls.

METHOD. The study group consisted of 47 preterm children (GA < 29 weeks, BW < 1000g; 26 boys and 21 girls) and 40 FT controls (17 boys and 23 girls). Bayley Scales of Infant Development (BSID-III) was used to assess the children's cognitive, language and motor skills at the corrected age two years. General and nonverbal intelligence were measured with Kaufman Assessment Battery for Children, 2nd edition (K-ABC-II) at the age of five years.

RESULTS. The PT group showed significantly lower scores for both outcome measures compared with the FT controls ($p = .02$ and $p < .001$). At the age of two years the PT and FT boys differed significantly in their cognitive and language scores ($p = .01$ and .02), but no differences between the groups were found for the girls. At the age of five general ability and nonverbal intelligence scores were lower for the PT boys ($p < 001$), but the FT girls outperformed the PT girls only in general ability scores ($p = .04$). The relationships between the early and later outcome scores varied across the assessed domains, genders and groups.

CONCLUSION. Early developmental outcomes have shown emerging difficulties for PT boys. Further assessment at preschool age is needed to detect developmental problems in PT children, especially girls.

The outcome of newborns with very low Apgar score at Tartu University Hospital in 2004-2014

Anne Antson[1], Karmen Meisalu[1], Jelena Kuznetsova[1], Heili Varendi[1,2] – [1]Tartu University Hospital, Tartu, Estonia; [2]Department of Pediatrics, University of Tartu, Tartu, Estonia

Very low Apgar score at birth may have different causes, including birth asphyxia, and sequelae. The International Classification of Diseases (ICD-10) states: P21.0: Asphyxia with 1-minute Apgar score 0-3. The level of acidosis at birth, presence and stage of hypoxic-ishaemic organ damage, incl. encephalopathy, are not mentioned.

The aim was to analyse the cases of neonates born with Apgar scores 0-3 at 1 minutes of postnatal age in order to define the incidence of severe asphyxia and unfavourable outcome.

METHODS. All newborns with the diagnosis of P21.0 born in 2004–2014 were identified from the database of Tartu University Hospital. Retrospective analysis of the electronic patient charts specified the detailed data (gestational age, Apgar scores at 5 and 10 minutes, pH and lactate from umbilical artery, fetal distress, clinical and radiological signs of hypoxic-ischaemic organ damage, background conditions, application of therapeutic hypothermia) and assessed data about child development.

RESULTS. The incidence of very low Apgar score in term newborns was 0.84% (199/23 827 births), in 10% of them Apgar score remained < 6 at 10 minutes (severe group). In the severe group, 80% of the babies developed convulsions and 70% were allocated to therapeutic hypothermia. Moderate, severe neurodevelopmental impairment or death occurred in 14% of all studied patients (40% in the severe group and 6.7% in the non-severe group) and the follow-up rate by paedatric specialists within the first years was only 35%.

CONCLUSIONS. Although the incidence of severe asphyxia among term infants with Apgar 0-3 at 1 minute was 10%, all infants with very low Apgar score might be at risk for developmental problems and should be seen by a specialist, at least within the first year of life.

Prevalence and mortality among children with spina bifida in Lithuania: an assessment in a European context from 1990 to 2010

Indre Bakaniene, V. Vasiliauskiene, Audronė Prasauskiene – Children's Rehabilitation Hospital Lopšelis affiliated to the hospital of Lithuanian University of Health Sciences

BACKGROUND. The prevalence of spina bifida throughout Europe varies from 1.1 to 6.39 per 10 000 live births. With advances in surgical and medical treatment, up to 90% of infants born with spina bifida survive until their first birthday. These children have significant chronic disability and complex health care needs.

AIM. To estimate the prevalence and five-year survival rate of children with spina bifida in Lithuania.

METHODS. In a retrospective study we identified all spina bifida cases in children born from 1990 to 2010 in Lithuania. The spina bifida prevalence and mortality rates were calculated. As the denominator, the number of live births was used. Data from our study were compared with the corresponding data available from EUROCAT and published studies.

RESULTS. The prevalence of spina bifida during the period from 1990 to 2010 in Lithuania was 3.3 per 10 000 live births. This estimate is 64% higher than the European average (2.2 per 10 000 live births) and up to 3 times higher than for the country with the lowest prevalence (France).

Infant mortality from spina bifida was 9%, and mortality within the first five years after birth was 13%. These mortality rates are higher than those reported from the most developed countries of Central and Western Europe.

CONCLUSION. Spina bifida remains a relatively common problem in Lithuania. At least 87% of children born with spina bifida can be expected to reach their middle childhood.

TEACHING COURSE V: DRUG RESISTANT EPILEPSY

NEUROIMMUNOLOGY

Contemporary and future management of patients with multiple sclerosis

Katrin Gross-Paju[1,2], Liina Vahter[1,3], Karin Kannel[1], Heigo Maamägi[1], Alar Kuusik[2] – [1]Clinic of Neurology, West-Tallinn Central Hospital, Tallinn, Estonia; [2]Tallinn University of Technology, Tallinn, Estonia; [3]Institute of Psychology, Tallinn University, Tallinn, Estonia

Multiple sclerosis (MS) is a relapsing-remitting autoimmune disease affecting young adults.

The aim of the study was to evaluate the importance of relapses on disease progression. Also, the feasibility of the wireless monitoring of motor functions was evaluated.

METHODS. The study group consisted of 170 consecutive MS patients. All participants were recruited from February 2010 to October 2013 (mean follow-up 2.3 years) from a single MS centre. The participants were evaluated at recruitment and on the first day during relapse visits and were followed up at 2 weeks, 1 month, 3 months and 6 months. The data from 183 relapses was obtained. Neurological disability was evaluated with EDSS. The cognition substudy included 147/170 MS patients. Neuropsychological test battery consisted of the Brief Repeatable Battery of Neuropsychological Tests, "Cowboy Story", Trail Making A, B and Bender Copies. Altogether 35 patients were evaluated using wireless sensor systems. Different sensor numbers, locations and motor tests were studied.

RESULTS. The EDSS score increased statistically significantly during relapses from 2.2 to 3.6 and remained at 3 during 6-month follow-up. All domains of EDSS including motor function, cerebellar, sensory and brainstem cerebral were impaired. Bladder function was the least affected. Cognitive functions were impaired in 20% of the patients during relapses. Only changes in verbal fluency during relapses were statistically significant. All functions were back on baseline in one month. The best location for wireless sensors was the belt region. Balance tests were the most sensitive.

CONCLUSIONS. Relapses influence motor outcome of patients with MS. However, relapses do not cause severe temporary or long term cognitive dysfunction. Senor systems are feasible to analyse neurological functions. The effect of treatments on MS relapses will be discussed.

The study was supported by the project EU47320 "Home monitoring system for neurodegenerative disease patients".

Pediatric multiple sclerosis: when we should doubt about diagnosis

Nerija Vaičienė-Magistris – Neurology Department, Medical Academy and Hospital of Lithuanian University of Health Sciences, Kaunas, Lithuania

MS in children is defined by a recent consensus definition which was issued in 2012 by the International Pediatric MS Study Group along with the definitions of ADEM and CIS. Application of the revised 2010 McDonald criteria in children enables to make an early diagnosis of MS and to initiate disease modifying therapies. However, the diagnosis of MS requires exclusion of other possible etiologies for CNS disturbance. The younger is the child and the more atypical are the presenting clinical, laboratory and neuroimaging features, the more doubt about diagnosis should be raised and the more care is needed in establishing the diagnosis. Atypical features include fever, encephalopathy, involvement of the peripheral nervous system or other organ systems, a progressive disease course, elevated erythrocyte sedimentation rate (ESR), marked CSF pleocytosis. Differential diagnosis includes a vast range of mimicking disorders: inflammatory diseases of the white matter such as immunogenetic diseases including primary or secondary hemophagocytic lymphohystiocytosis, acute encephalopathies with autoantbodies, vasculitis, lymphoma, as well as infectious, genetic, metabolic and tumor diseases. Majority of disorders in this spectrum are very rare, many of them respond to treatment with steroids, which makes diagnosis even more complex. A minimal diagnostic testing battery for a child suspected of having MS should include brain and spinal cord MRI, CSF studies, visual evoked potentials, ESR and ANA. Expanded evaluation should be based on specific clinical presentation. In case the diagnosis of MS is already established and even if the child receives disease modifying treatment, doubt should be maintained and a special attention should be paid if the child is young, if there occurs any new involvement outside CNS, and if the course of the disease is actively relapsing or progressive despite treatments.

Challenges in diagnosis of autoimmune encephalitis in children

Inga Talvik[1,2], Aita Napa[1], Ulvi Vaher[1], Katrin Gross-Paju[3] – [1]Children's Clinic of Tartu University Hospital, Tartu, Estonia; [2]Department of Pediatrics, University of Tartu, Tartu, Estonia; [3]West Tallinn Hospital, Tallinn, Estonia

Encephalitis refers to an inflammatory disorder of the brain resulting in altered mental status, seizures, or focal neurologic deficits. The diagnosis of neuroinfection is based on signs of inflammation in the cerebrospinal fluid and magnetic resonance imaging (MRI) findings. Most patients undergo extensive testing for infectious etiologies without discovery of a causative agent. A study by the California Encephalitis Project, a center focusing on the epidemiology and etiology of encephalitis, found that 63% of the patients remained without an etiology after a battery of tests for 16 potential infectious agents. During the last 10 years a new group of diseases, autoimmune encephalitis, has emerged. Although a number of specific autoantibodies have been described, it is recognized that no antibodies have been discovered nor commercial assays are available.

We report the diagnostic process of a 4-year-old boy with encephalitis of unknown origin. After extensive testing the diagnosis of autoantibody negative encephalitis was made. The EEG findings were most informative leading to the diagnosis of antibody negative encephalitis. We describe remarkable recovery of the patient with the use of immunotherapy.

Conclusions. Over the past decade, it has become increasingly recognized that autoimmune conditions contribute significantly to the spectrum of the causes of encephalitis. Clinical suspicion and early diagnosis of autoimmune encephalitis are of particular importance because of the availability of effective treatment.

It is relatively easy to make the diagnosis when autoantibodies are positive, but it is a challenge when commercially available assays are negative.

Clinical case presentation of LGI1 antibody positive encephalitis

Katrin Gross-Paju[1,2], Liina Vahter[1], Ulvi Sorro[1], Agnes Reitsnik[1], Karin Kannel[1] – [1]West-Tallinn Central Hospital, Tallinn, Estonia; [2]Institute of Clinical Medicine, Tallinn University of Technology, Tallinn, Estonia

A 35-year-old female patient was admitted with spells of a „tingling feeling" on the nose and the forehead region, „strange taste" and smell sensations and bright colourful images with *deja vu* feeling. She had experienced approximately 100 attacks, lasting 20–60 seconds per day since 26.02.2013. After the attack she felt tired, complained of memory problems, clumsiness in the right hand and paranoid thoughts.

The patient had had a similar tingling feeling with a duration of 3–4 seconds 1–2 times per month for years, which had not been disturbing.

Clinical evaluation demonstrated no focal neurological signs, paranoid thoughts, but no cognitive deficits in extensive neuropsychological testing.

EEG showed focal epileptic activity in the right temporal region. MRI of the brain was completely normal. Routine clinical workup was unremarkable. Serum LGI1 antibodies were positive (LGI1 IgG positive 1:32).

The patient was diagnosed with autoimmune encephalitis with voltage-gated potassium channel (VGKC)–complex-associated LGI1 autoantibodies. She was treated with methylprednisolone pulse therapy 1 g x 5 i/v. After the treatment all her symptoms resolved and her repeated EEG was normal.

VARIA

Abusive head trauma

Randell Alexander – Division of Child Protection and Forensic Pediatrics, University of Florida, Jacksonville, USA

Abusive head trauma (AHT) has an incidence of between 10 to 40 per100,000 infants, but is the leading cause of death and serious disability from child physical abuse. Mortality is between 20–25% and most survivors have significant motor, visual, and/or cognitive deficits.

This session will review current thinking about the mechanisms of injury with abusive head trauma. The risk factors, epidemiology, and outcomes will be examined. Examples will be given about elements of diagnosis. Alternative hypotheses are sometimes made – particularly in the court settings. However, there is no natural mimic of children who are shaken. Ultimately, prevention of AHT is the goal and various strategies will be discussed.

Novel homozygous mutation in *KPTN* gene causing familial intellectual disability-macrocephaly syndrome

Sander Pajusalu[1,2], Tiia Reimand[1,2,3], Katrin Õunap[1,3] – [1]Department of Genetics, United Laboratories, Tartu University Hospital, Tartu, Estonia; [2]Institute of Biomedicine and Translational Medicine, Department of Biomedicine, University of Tartu, Tartu, Estonia; [3]Department of Pediatrics, University of Tartu, Tartu, Estonia

BACKGROUND. Recently, Baple et al. (*Am J Hum Genet* 2014, 94(1):87–94) described a large Amish pedigree where homozygous or compound heterozygous mutations in *KPTN* gene encoding kaptin protein resulted in a clinically distinctive syndrome consisting of macrocephaly, global developmental delay, behavioural abnormalities, and seizures (MIM 615637). Here we report the second case of *KPTN*-related syndrome in two Estonian siblings with novel homozygous *KPTN* mutation and a similar phenotype.

CASE REPORT. The probands are 32-year-old brother and his 24-year-old sister from Estonia. The parents are non-consanguineous but were born in the same parish. The brother and sister have macrocephaly, with an occipitofrontal circumference of 63 cm (+4.5 SD) and 60 cm (+4 SD), respectively. Their intellectual disability could be classified as moderate. The verbal abilities are more affected than motor development in both siblings. Behavioural problems and epilepsy have been present only in the brother.

METHODS AND RESULTS. Whole exome sequencing identified homozygous one-nucleotide frameshift duplication in *KPTN* gene (c.665dupA:p.Q222fs). Homozygosity of both affected siblings and heterozygosity of the parents was confirmed by Sanger sequencing. SNP-array showed a 1.5 Mb homozygous stretch encompassing *KPTN* gene in both siblings.

CONCLUSIONS. With this report we confirm the pathogenicity of *KPTN* gene mutations and delineate the core phenotype of the novel autosomal recessive genetic syndrome. We also support the hypothesis of the authors of the first description that *KPTN*-related syndrome is not restricted to the Amish population.

This work was supported by the Estonian Research Council grant PUT355.

Familial porencephaly – clinical and neuroimaging manifestations in persons with *COL4A1* gene mutation

Kristi Simenson[1], Ülle Krikmann[2], Tiiu Tomberg[3], Ülle Murumets[1], Neeme Tõnisson[1], Katrin Õunap[1,4] – [1]Department of Genetics, United Laboratories, Tartu University Hospital, Tartu, Estonia; [2]Neurology Clinic, Tartu University Hospital, Tartu, Estonia; [3]Radiology Clinic, Tartu University Hospital, Tartu, Estonia; [4]Department of Pediatrics, University of Tartu, Tartu, Estonia

Mutations in the *COL4A1* gene have been found to cause autosomal-dominant porencephaly and leukoencephalopathy. Additionally, infantile hemiplegia, migraines, seizures, intracerebral hemorrhage, ischaemic stroke, hematuria, arrhytmias may occur. We report here a family with a novel *COL4A1* gene mutation and a different clinical phenotype.

The index patient is a 50-year-old woman who has had migraine like headaches during the last 5 years, hypertension since she was 30, and microhematuria and unspecified eye damage since childhood. Last year she suffered a transitorial ischaemic attack. Brain MRI showed left frontal horn porencephalic enlargement of the lateral ventricle, leukoencephalopathy and small T-2 hyperintensities in area of the basal ganglia. A novel heterozygous mutation (c.1826G>A, p.Gly609Asp) was identified in the *COL4A1* gene. This mutation has not been described previously, but is predicted to be pathogenic because Gly substitution hampers the formation of the triple helix. Patient's daughter (25y) had congenital hydronephrosis, but no other symptoms, and nonspecific MRI findings. Patient's son (20y) had a subclinical stroke in the perinatal period and an episode of supraventricular tachycardia at age 2 months. His physical and mental development is normal. His MRI is similar to that of the mother. He has arrhythmic episodes and frequent epistaxis and he becomes easily tired. Patient's sister (30y) has had severe headaches during the last 10 years. Patient's mother died from cerebral infarction at age 69. Their genotypes have not been investigated.

It is noteworthy that the patient's phenotype is quite mild and her daughter has no complaints although she carries the same mutation. Consequently, the clinical picture among *COL4A1* gene mutation carriers can be very variable.

Joubert syndrome - an example of ciliopathy. A family case presentation

Riina Žordania[1], Haide Põder[2], Konstantin Ridnõi[3], Anneli Kolk[4], Kairit Joost[1] – [1]Department of Genetics, United Laboratories, Tartu University Hospital, Tartu, Estonia; [2]Tallinn Children's Hospital, Tallinn, Estonia; [3]Perinatal Care Centre, Women's Clinic, East-Tallinn Central Hospital, Tallinn, Estonia; [4]Department of Pediatrics, University of Tartu, Tartu, Estonia

INTRODUCTION. Ciliopathies are a heterogenic group of disorders caused by abnormal formation and function of the cilia. This causes a severe multisystemic disease with frequent involvement of the brain, eye and kidneys. Joubert syndrome (JS) is a rare autosomal recessive ciliopathy that affects the cerebellum. The key finding of cerebellar vermis hypoplasia is the molar tooth sign (MTS) on axial MRI images. Up to now cilipathies are associated with over 40 genes, including 24 genes responsible for the development of JS.

AIM is to present a family case of Joubert syndrome. Diagnostic problems, the algorithm and literature data are discussed.

RESULTS. The index patient was a 3-month-old boy who had hypotonia, developmental problems, and operated postaxial unilateral polydactyly and changes in the retina. Preliminary genetic investigations revealed no disease associated changes. As the patient's brain MRT revealed MTS, JS was diagnosed. However, sequencing of genes *AHI1, CEP290, NPHP1* displayed no disease associated variants. Prenatal diagnosis during subsequent pregnancy was performed by fetal ultrasound investigation. It showed MTS, which was confirmed by fetal brain MRI. Finally, a next generation sequencing (NGS) panel involving 24 genes associated with JS was performed and three heterozygous mutations in gene *C5orf42* were revealed: c.2377C>T in exon 13, c.9058C>T in exon 49, c.1096C>T in exon 9 (variant of unknown significance). Based on the results, JS type 17 was diagnosed.

CONCLUSION. If antenatal diagnosis cannot be made by genetic means, fetal brain radiologic investigations will be informative for the prenatal diagnosis of JS.

NGS panel analysis is helpful in the clinical diagnosis of heterogenic disorders in case the clinical picture is defined.

Methods of intraoperative neurophysiology

Kaidi Lunge – Tallinn Children's Hospital, Tallinn, Estonia

The principal goal of all forms of intraoperative monitoring (IOM) is to prevent new neurologic impairment by identifying it sufficiently early to allow prompt correction of the cause. Intraoperative neurophysiologic monitoring during different operations is now a routine method at many centers.

We started IOM during scoliosis surgery at Tallinn Children's Hospital in 2004 and since then we have performed over 700 monitorings. At present we are advancing in the field of intraoperative neurophysiology in neurosurgical operations.

The main methods and different techniques of intraoperative neurophysiology will be described.