CLINICAL FRONTIERS
IN PEDIATRIC NEUROLOGY 2019

SCIENTIFIC PROGRAMME
and
ABSTRACT BOOK

October 17th–18th, 2019
Grand Hotel Union, Ljubljana, Slovenia
SCIENTIFIC PROGRAM COMMITTEE

Slovenia: Dr. Neli Bizjak, Prof. dr. David Neubauer, Doc. dr. Damjan Osredkar
Prof. Zvonka Rener Primec, As. dr. Mirjana Perković Benedik,

Croatia: Prof. dr. Nina Barišić, Doc. dr. Radenka Kuzmanić Šamija, Prof. dr. Igor Prpić,

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ORGANISING COMMITTEE


ABSTRACT BOOK DESIGN: Rok Kučan.

ORGANISED BY

Department of Child, Adolescent and Developmental Neurology University Children's Hospital Ljubljana, Slovenia &
Department of Pediatrics, Medical Faculty, University of Ljubljana.
Under the auspices of EPNS.
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Preface

Dear Friends and Colleagues,

we will gather in Ljubljana to enjoy the Clinical Frontiers in Pediatric Neurology, on October 17 and 18, 2019.

This congress, which we hope will become a recurring annual meeting, will bring together physicians, health professionals and scientists from the Alpe-Adria region, Europe and from around the world. We will provide numerous networking opportunities and knowledge exchange! We will proudly disseminate the latest progress in our exciting and increasingly diverse array of activities in the field of pediatric neurology, all focused on improving the well-being of children with neurological diseases. We will celebrate the extraordinary research advances in our field – witnessing pediatric neurology at the forefront in the remarkable times of medical progress. We will think about new treatments and strategies, as well as the impact, burden and cost of diseases in the field of pediatric neurology for the individual and society.

We sincerely look forward to welcoming you to our congress in 2019.

Damjan Osredkar, MD, PhD
Head of Organising Committee CFPN
## SCIENTIFIC PROGRAMME: Thursday, October 17th, 2019

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| 10.45 – 13.20| Epilepsy<br>Chairpersons: Ružica Kravljanac, Mirjana Perković Benedik      | Sameer Zuberi<br><strong>Aetiology & Epidemiology of Epilepsy: a 21st Century Perspective</strong>  
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**SCIENTIFIC PROGRAMME: Friday, October 18th, 2019**

**Open Section Chairperson: Igor Prpić**

8.30 – 9.00 Registration
9.00 – 10.40 Open Section
9.00 – 9.20 Evgen Benedik
   *All you need to know about a diet of children with autism spectrum disorder*
9.20 – 9.40 T Golli, Z Rener Primec
   *Neurofibromatosis – an epidemiological overview and therapeutic algorithm*
9.40 – 10.00 Barbara Gnidovec Stražišar
   *Sleep related disorders in children*
10.00 – 10.20 Maja Đorđević Milošević
   *Neurological manifestations of mitochondrial disorders*
10.20 – 10.40 Uroš Krivec
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10.40 – 10.55 Coffee break
10.55 – 11.55 Immune-Mediated Neurological Diseases and Congenital Myasthenic Syndromes
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10.55 – 11.15 Neli Bizjak
   *Clinical characteristics of Slovene children with multiple sclerosis*
11.15 – 11.35 Vesna Branković
   *Immune mediated cerebellar ataxias in children*
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   *Congenital myasthenic syndromes*
11.55 – 13.00 Lunch break
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| 13.00 – 14.50 | **New Diagnostic and Treatment Possibilities**  
Chairperson: Radenka Kuzmanić Šamija |
| 13.30 – 13.50 | **Slovene cohort of patients with refractory epilepsy treated with cannabidiol**  
Duma F, Sabolic V, Muaremoska Kanzoska Lj, Alili Ademi L, Milenkova L |
| 13.50 – 14.10 | **Practical experiences and perceptions of the Effects of Kanobil Epi as an add-on treatment in refractory epilepsy in children**  
Aleš Maver |
| 14.10 – 14.30 | **Significance of novel genomic technologies in diagnostics of pediatric neurologic disorders**  
Neli Bizjak |
| 14.30 – 14.50 | **Gilenya, the first and only oral disease-modifying treatment for children and adolescents with MS**  
Sponsored lecture |
| 14.50 – 15.05 | **Coffee break**                                                                                                                                 |
| 15.05 – 16.00 | **Thieves Market: Interesting Clinical Cases**  
Chairperson: David Neubauer |
| **Case #1** | **A girl with an atypical form of Dravet Syndrome** |
| **Case #2** | **Idiopathic (benign) intracranial hypertension – is it really benign condition?** |
| **Case #3** | **Epileptic encephalopathy caused by a novel heterozygous variant of VARS2 gene mutation** |
| **Case #4** | **Rare mutation of Congenital Myasthenic Syndrome** |
| **Case #5** | **Impact of epileptiform activity on cognition** |
| **Case #6** | **Opsoclonus-myoclonus Syndrome – a case report** |
| 16.00 | **Closing Remarks** |
Paroxysmal Eye Movement Disorders in Children

Oražem Mrak J, Neubauer D

1 University of Ljubljana, Medical Faculty and University Medical Centre, Children's Hospital, Dept. of Child, Adolescent & Developmental Neurology, Ljubljana, Slovenia

Due to vision being such an important feature in human existence, eye movement neurology is a big and extensively studied field. Mechanisms of the four basic types of eye movements (saccades, smooth pursuit, vergence and vestibulo-ocular movements) are additionally complex in pediatric population, each having its own developmental characteristics. Abnormalities in their expression represent an important clue to what kind of pathological process is happening in the nervous system and to its potential location.

Paroxysmal abnormal eye movements are a common cause of referral for pediatric neurological assessment, largely under suspicion of being epileptic seizures. Very often they represent one of the transient benign paroxysmal movement disorders of infancy (paroxysmal tonic upgaze of childhood, paroxysmal tonic downgaze of newborn and infancy/benign positional vertical opsoclonus) or are part of a complex developmental movement disorder (tics, stereotypies). Some entities can be transient benign or potentially symptomatic, ie. paroxysmal nystagmus, spasmus nutans. A whole spectrum of pathologies can manifest themselves with opsoclonus, however diagnostic and treatment implications require quick recognition of opsoclonus-myoclonus-ataxia syndrome. Correctly identified impaired eye movements (aberrant saccades, gaze palsies, oculomotor apraxia,..) can often aid initial diagnosis (ie. Nieman-Pick type C, Friedreich ataxia, Ataxia-telangiectasia,..). In addition, abnormal eye movements are sometimes an initial manifestation of complex genetical neurological conditions, with concurrent developmental delay or regression and/or epilepsy, such as GLUT1 deficiency or disorders caused by mutations in CACNA1A.
A Contemporary View of Pediatric Functional Neurological Symptoms: Integrated Etiological Models and their Treatment Implications

Gosar D, Stropnik S, Meško T, Lešnik-Musek P, Krkoč V

1 University Medical Centre, Children's Hospital, Dept. of Child, Adolescent & Developmental Neurology, Ljubljana, Slovenia

Although relatively rare in the general population of children and adolescents (yearly incidence of 1.30/100000) functional neurological disorders have a high prevalence in the pediatric neurology setting and often require significant medical resources and diagnostic workup. Furthermore, they lead to emotional distress and significant limitations in a family’s life, engender stigma and expose patients to increased risk of iatrogenic harm. Throughout the previous century functional symptoms were often label as "hysterical" and were mostly seen to be the consequence of unresolved psychological conflicts and trauma. Current etiological models offered a more nuanced view. Based on research during the past two decades they point out the significant heterogeneity among such patients, both in term of potential predisposing risk factors (previous psychological trauma and increased prevalence psychiatric symptoms, general tendency to experience unexplained somatic symptoms, previous exposure to illness symptoms in self and others, increased hypervigilance) as well as reinforcing factors (assuming a sick role, getting secondary gain). They emphasize that at the individual level functional neurological symptoms can be best understood as a specific combination of these factors. Going a step further some authors (Seth and Friston, 2016; Van den Bergh et al., 2017) propose going beyond this type of bio-psycho-social models. They see functional symptoms as a more general manifestation of the way our brain constantly attempts to interpret our interoceptive environment and other sensory input based on previous expectations and beliefs. Building on Bayesian statistics they highlight that in both health and disease our conscious awareness of somatic symptoms reflects an interplay between context, the precision of incoming sensory information and the precision and type of our prior expectations. Thus, they see functional symptoms not as a
mental disorder, but rather the extreme of a normal dimension of subjective somatic symptom experience. Reinterpreting functional symptoms in this way has significant implication for both communicating with patients and treating them. It highlights the importance of shaping expectations, as well as points towards new avenues of treatment, that compliment currently established cognitive behavioral treatment models.

Clinical Spectrum Between Epilepsy and Movement Disorders

Stevanovic G¹

¹ Clinic of Neurology and Psychiatry for Children and Youth, Belgrade, Serbia

Similar clinical picture and overlapping phenomenology in epilepsy and movement disorders, make differential diagnose challenging in some conditions (eg paroxysmal dyskinesias, frontal lobe seizures, status dystonicus, startle reaction, myoclonus). New era of available genetic testing revealed heterogeneous and more complex genotype-phenotype correlation broadening spectrum of clinical picture in many well known and defined disorders (eg AHD, Dravet sy, PRRT2) . Phenotypic pleiotropy could be explained by the type and timing of mutations during development, various gene expression, influence of epigenetic factors and gene modifiers. Shared genetic etiology in early-onset epileptic encephalopathies and movement disorders usually with co-existence of developmental disability (eg SCN1A, SCN8A, CACNA1A, ATP1A2/3, STXBP1, ARX, mitochondrial disorders) makes prediction of prognosis difficult. Different pathophysiological mechanisms are proposed , describing dysfunction of ion channels, signal transducing processes, cell adhesion, transporters and receptors changes, pointing out not only to already well known concepts of channelopathies, inborn metabolic disorders but also introducing new terminology as synapthopathies, proteinopathies, developmental interneuronopathies, tubulinopathies etc. Finding a definitive, genetic cause is undoubtedly important from different points of view. Specific therapy, targeting the pathophysiology of the condition or reducing toxic accumulation is possible in some neurometabolic disorder (eg. Glut 1 deficiency,
FOLR1 mutation), where timing of the therapy plays a crucial role in further prognosis. Symptomatic treatment can be influenced by the genetic origin (e.g. stiripentol for SCN1A), sometimes requiring assessment of functional activity (e.g. phenytoin in SCN8A mutation with gain-of-function). Genetic counseling and implication of comorbidity on everyday life are equally important issues.

Status Epilepticus as the First Epileptic Event in Children

Kravljanac R¹, Vučetić Tadić B¹, Kovačević G¹, Ostojić S¹, Pekmezović T¹

¹ Institute for Mother and Child Healthcare of Serbia, Belgrade; Institute for Epidemiology, Faculty of Medicine, University of Belgrade

Status epilepticus (SE) is a condition resulting, either from the failure of the mechanisms responsible for seizure termination, or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point 1), and can have various long-term consequences (after time point 2). For convulsive SE, time point 1 is 5 min and time point 2 is 30 min.

Purpose: Evaluation of the etiology, clinical characteristics and outcome of the first status epilepticus (fSE) as the first epileptic event in children. Method: The children with fSE treated in our Institute (1995-2011) were included. Outcome was assessed at the end of hospitalization. Logistic regression analyses were used to assess predictors of the outcome. Results: The study included 236 patients with a median age of 2.0 years (IQR 4.0). Estimated etiology: defined electroclinical syndromes 108 (45.8%), acute symptomatic conditions 63 (26.7%), unknown 24 (10.1%), progressive encephalopathy (PE) 23 (9.7%), or remote symptomatic 18 (7.6%). Outcome was: recurrence rate 16.9%, neurological consequences 24.6% and case-fatality ratio 4.7%. The main predictors were for: a) death – progressive encephalopathy (OR=14.68, 95%CI 4.06–23.11. p=0.001); b) neurological consequences – acute symptomatic (OR 3.44, 95%CI 4.82–6.47) p=0.001, remote symptomatic (OR=13.84, 95%CI 4.34–44.12. p=0.001), progressive encephalopathy (OR=3.94, 95%CI 1.64–9.56. p=0.002), seizure duration >60 min (OR=0.44, 95%CI 0.24–0.81. p=0.001); c) seizure recurrence – acute
symptomatic etiology (OR=3.59, 95%CI 41.76–7.21. p=0.001), seizure duration >60 min (OR=0.30, 95%CI 0.15–0.61. p=0.001). Conclusions: fSE is common among all the children with SE. Febrile SE represents the largest etiology subgroup, followed by acute symptomatic SE, attributed primarily to CNS infections. A large proportion had SE with a duration >60 min. Etiology and fSE duration are the main determinants of fSE outcome. In the clinical approach to patients with fSE, it is important to explore the underlying, mostly acute disorders, since concomitant therapy is important and may have significant impact on the clinical outcome.

Management of Dravet syndrome in Slovenia

Perkovic Benedik M¹, Bizjak N¹, Osredkar D¹, Neubauer D¹

¹ University Children’s Hospital Ljubljana, Department of Child, Adolescent and Developmental Neurology, Ljubljana, Slovenia

Background: Dravet syndrome (DS) is a severe infantile-onset epileptic encephalopathy characterized by drug-resistant epilepsy accompanied by cognitive, and motor impairment. 70-85% of patients with DS have mutations in the SCN1A gene. Diagnostic criteria for DS include seizure onset in infancy, mainly triggered by fever and often prolonged; later occurrence of other seizure types, normal motor and cognitive development prior to seizure onset with subsequent slowing including plateauing or regression of skills. Electroencephalography (EEG) recordings during the first year are usually normal, but from the second year background activity becomes slow in 50% of patients, and paroxysmal epileptiform EEG abnormalities can be recorded. Dravet syndrome remains largely pharmacoresistant to antiepileptic drugs, the combination of stiripentol with valproate and/or clobazam is considered to be one of the most useful.

Purpose: The aim of this study was to describe specific clinical features of Dravet syndrome in Slovenian children. Our department is the referral center for rare and difficult to treat epilepsies for the whole country and the majority of the children with Dravet syndrome from Slovenia are treated at our department.

Method: We retrospectively reviewed the medical records of all
pediatric patients who were diagnosed with Dravet syndrome between 1st January 1998 and 31st December 2018.

Results: The clinical data of 15 DS patients (4 males, 11 females) were reviewed. The median age at seizure onset was 6 months (range 4-8 months) and the median age at diagnosis was 2.6 years (range 0-17 years). A mutation in the SCN1A gene was found in all 15 patients (100%). All children had febrile seizures. Among these 6 (40%) presented with febrile seizures as the first symptom of the disorder. Stiripentol, as add-on medication was used in 11 patients.

Conclusions: This is the first analysis of a cohort of patients with Dravet syndrome in Slovenia, which represents the majority of Dravet patients in Slovenia. Two prolonged or febrile seizures in the first year of life should raise suspicion of Dravet syndrome, and genetic testing should be performed to achieve early and correct diagnosis, leading to an adequate treatment and better outcome.

Sudden Unexpected Death in Epilepsy (SUDEP): Risk Factors, Mechanisms and Prevention

Barišić N

1 Department of Paediatrics, Clinical Medical Centre Zagreb, University of Zagreb Medical School

Background. Sudden Unexpected Death in Epilepsy (SUDEP) is defined as sudden, unexpected, witnessed or unwitnessed death of patients with epilepsy, with or without preceding seizure excluding status epilepticus, and in whom autopsy does not reveal a structural or toxicological cause of death and excludes prior trauma or drowning.

Results and Discussion. SUDEP is a major cause of epilepsy-related mortality. Reported SUDEP incidence in children (0-17 years) with epilepsy is 0.22-1.17/1,000 patients. Up to 50% of patients with pharmacoresistant epilepsy die of SUDEP. SUDEP incidence is higher for paediatric patients with early onset epilepsy before the age 5 years compared to adults. Epilepsy surgery candidates and Dravet syndrome patients are at the highest risk for SUDEP with an incidence of 9.1 and 9.3 SUDEP deaths per 1,000. The SUDEP event sequence starts with seizure (generalized or focal) followed by increased respiratory rate, and subsequently apnea, bradycardia, and cardiac
arrest with concomitant generalized EEG suppression. The pathophysiology and possible mechanisms of SUDEP involves large number of factors such as loss of arousal, time of day, position of the patient during the seizure, autonomic dysfunction and combined failure of respiratory and cardiovascular control. Certain genetic mutations may predispose patients with epilepsy to SUDEP via central or peripheral nervous system or end-organ effects. Preventive strategies for SUDEP include seizure control, advice on lifestyle factors, respiratory and heart rate monitoring devices, preventing airway obstruction by nocturnal supervision, enhancing serotonergic mechanisms, decreasing the possibility for missed doses of antiepileptic drugs and by reducing adenosine level and brainstem depression.

Conclusion. Increased understanding and awareness for SUDEP and possible prevention measures emphasize necessity to inform the parents/families and patients with epilepsy about SUDEP in order to reduce known risks and potentially to save patients’ lives.

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**Genetic Testing in Children with Epilepsy – A Croatian Tertiary Center Experience**

Prpić I¹, Radić Nišević J¹, Kolić I¹, Borovečki F²

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Introduction: The application of new genetic methods, primarily Chromosome Micro Array (CMA), as well as Next Generation Sequencing (NGS) reveals an increasing number of genes responsible for the etiology of epilepsy. Aim: This study documents the results of performed CMA and NGS on children with epilepsy, generally pharmaco-resistant ones and/or etiologically undefined epilepsy, with or without accompanying symptoms (i.e. developmental delay, autism spectrum disorders and/or multiple congenital anomalies). Methods: The research was conducted retrospectively at the Department of Pediatrics, University Hospital Centre (UHC) of Rijeka (Croatia) from June 2016 to January 2019.
The blood samples were analysed at the Functional Genomic Department of UHC Zagreb (Croatia), Children's Hospital Zagreb (Croatia), CeGaT Tübingen (Germany) and Blueprint Genetics in Helsinki (Finland).

Results: The diagnostic yield of CMA in our study was 18%, while the diagnostic yield of the genetic panels was 39%. Conclusion: CMA and/or NGS techniques (whether epilepsy panel or whole exome sequencing) represent a valuable diagnostic tool in contribution to etiological diagnosis of epilepsy. Nowadays, these methods should be the first-choice diagnostic option for patients with undefined and/or pharmaco-resistant epilepsy with or without additional neurodevelopmental disorder. The obtained results allow the use of more specific and personalized treatment, which significantly contributes to the patient’s wellbeing. Furthermore, this data expands our general knowledge regarding the etiology of epilepsy and reveals the phenotype-genotype correlation in children with epilepsy.

Diagnostic Dilemmas of MRI in Pseudotumor Cerebri

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Intracranial hypertension is a general term indicating elevated intracranial pressure. It can be primary or secondary due to space occupying lesions, hydrocephalus, etc. The primary form, also known as idiopathic intracranial hypertension (IIH) or pseudotumor cerebri (PTC), is a clinical entity characterized by headache and vision disturbances. The disease is typical for obese middle-aged women, but children may be affected as well. Historically imaging was done to exclude other pathology, while currently MR imaging protocols enable us to study subtle signs that are thought to indicate the disease. In the absence of other causes of elevated intracranial pressure, imaging findings that support the diagnosis of PTC are partially empty sella turcica, stenosis of the lateral segments of both transverse sinuses, prominent subarachnoid space around orbital part of the optic nerves and vertical tortuosity of the optic
nerves, flattening of the globes with possible intraocular protrusion of the optic nerve head and also some other, less specific signs. Transverse sinus stenosis appears to be the most useful sign with high specificity and fairly high sensitivity. Four of the MRI markers are also included in the modified Dandy criteria for PTC, without papilledema and abducens nerve palsy. The sensitivity of these markers is moderate, especially in prepubescent children (Imaging Features of Idiopathic Intracranial Hypertension in Children; Hartmann et al.), so the absence of these findings does not completely rule out PTC. On the other hand, it’s still not completely clear whether these findings assist clinicians in establishing the diagnosis of PTC or generate a number of overdiagnoses and therefore unnecessary procedures. Intracranial hypertension is a general term indicating elevated intracranial pressure. It can be primary or secondary due to space occupying lesions, hydrocephalus, etc. The primary form, also known as idiopathic intracranial hypertension (IIH) or pseudotumor cerebri (PTC), is a clinical entity characterized by headache and vision disturbances. The disease is typical for obese middle-aged women, but children may be affected as well. Historically imaging was done to exclude other pathology, while currently MR imaging protocols enable us to study subtle signs that are thought to indicate the disease. In the absence of other causes of elevated intracranial pressure, imaging findings that support the diagnosis of PTC are partially empty sella turcica, stenosis of the lateral segments of both transverse sinuses, prominent subarachnoid space around orbital part of the optic nerves and vertical tortuosity of the optic nerves, flattening of the globes with possible intraocular protrusion of the optic nerve head and also some other, less specific signs. Transverse sinus stenosis appears to be the most useful sign with high specificity and fairly high sensitivity. Four of the MRI markers are also included in the modified Dandy criteria for PTC, without papilledema and abducens nerve palsy. The sensitivity of these markers is moderate, especially in prepubescent children (Imaging Features of Idiopathic Intracranial Hypertension in Children; Hartmann et al.), so the absence of these findings does not completely rule out PTC. On the other hand, it’s still not completely
clear whether these findings assist clinicians in establishing the diagnosis of PTC or generate a number of overdiagnoses and therefore unnecessary procedures.

Clinical Presentation of Pompe Disease in Children


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Introduction: Pompe disease (PD) is a rare progressive muscular disease also known as glycogen storage disease type II, due to mutations in the gene coding for acid alpha-glucosidase (GAA). Mutations that decrease the activity of this enzyme lead to the accumulation of glycogen in the lysosomal compartment and to the impairment of lysosomal function and autophagy. According to that, glycogen accumulates virtually in all tissues, but the disease manifestation is prominently muscular, with proximal muscle weakness, severe hypertrophic cardiomyopathy and respiratory function impairment. Purpose: A variety of the clinical spectrum of PD in childhood and differential diagnosis. Results: We diagnosed 4 patients in Mother and Child Health Care Institute of Serbia during last 5 years. Two patients had early infantile onset of Pompe disease (IOPD) and two sisters had juvenile form of late onset Pompe disease (LOPD). IOPD manifested with severe generalized hypotonia in the first months of children's life, hypertrophic cardiomyopathy and increased level of creatine kinase (CK) in blood. The course of disease was very progressive, leading to death in the first year of life due to cardio-respiratory failure in one child. Another child with IOPD lived for 4 years on continued mechanical ventilation, 1.5 years in our hospital, and after that at home. She received enzyme therapy (“Myosime”). Children with LOPD have slower progressive disease, without
respiratory and cardiac involvement. Hypomimia and paravertebral muscles weakness were only deviations in infant period. The more pronounced proximal muscle weakness, waddling gait and the pseudohypertrophy of the calf muscles were present at the age of 3 years. Level of CK varied in the range of 2-10 times higher than reference values. Needle EMG has recorded myotonic discharges and myopathic potentials in the distal extremities muscles. Reduced activity of GAA in blood was an indication for genetic analysis, which confirmed Pompe disease in all patients. Sisters with LOPD don't receive enzyme therapy. Conclusion: The onset and progress of PD can occur from birth to late adulthood. There is a great variability in phenotypes of the disease regarding the age of the symptoms onset and the degree of organ involvement. The possibility enzyme therapy have made a major improvement in the morbidity and mortality of PD. New therapies are also in development, so that early recognition and diagnosis of PD is important.

Childhood CNS Tumors in Slovenia – Relation to Patient and Tumor Characteristics

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Central nervous system (CNS) tumors are the most common solid tumors and the leading cause of cancer-related death in children. They include several histologic subtypes. The incidence varies by country from 1,12 to 5,14 cases per 100,000 persons. In Slovenia, all children with cancer are treated in a single referral centre – Department of Paediatric Haematology and Oncology in Children's University Hospital in Ljubljana, with a mandatory registration of all oncology patients in the National Cancer Registry. Paediatric neurologists are mostly involved in the initial diagnosis of children with CNS tumors and in the further management of children with low grade glioma (LGG).
The aim of this study was to identify patient and tumor characteristics in Slovenian population in last 12 years, also with the purpose for a closer look at managing a group of patients with LGG. As in similar studies from other countries, we found, CNS tumors are more common in males, though this varies by histologic type. Gliomas are the most common CNS tumors and medulloblastoma is the most common malignant brain tumor among children. The presenting neurological symptoms noted in our study were headache, vomiting and visual defects as manifestations of intracranial hypertension and seizures, walking instability and other focal neurological signs regarding tumor location. We found out that population of LGG patients was growing in last decade, possibly due to increased availability of MRI, multidisciplinary approach and more careful patient registration. Regarding the management of LGG patients, we believe that national recommendations of follow up would be necessary to unify.

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**Therapy Development in Neuromuscular Disorders**

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Improved insights in the etiology, biology and genetics of neuromuscular disorders has fueled the development of therapies for these diseases. Therapeutic strategies targeting the underlying cause of diseases or the downstream cascade of events have moved from pre-clinical to clinical development, some of them being yet approved by regulatory authorities. Promising strategies that could impact on disease progression have raised hope for Duchenne Muscular Dystrophy, however, the journey to a real treatment has shown to be long. The disappointment from failed trials has not halted research. Novel strategies and new generations of therapeutic molecules are currently in development. The most spectacular advances have been made in the field of Spinal Muscular Atrophy, where splicing modifiers and gene therapy have been approved as treatment. We will review the latest stage of therapy development, the
emerging experience with these new therapies and discuss the challenges faced in therapy development for neuromuscular diseases.

Evaluation of Slovenian Children with Spinal Muscular Atrophy Type I-III 420 Days After Treatment with Nusinersen

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Introduction: Spinal muscular atrophy (SMA) is characterized by muscle weakness, atrophy and paralysis. Nusinersen is an antisense oligonucleotide, designed to alter splicing of SMN2 pre-mRNA and thus increase the amount of functional survival motor neuron protein in SMA patients. Aims: To evaluate a motor - milestone response defined according to the results of The Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders - CHOP – INTEND, Hammersmith functional motor scale (HFMS) and treatment adverse events (AE). Methods: We conducted a prospective, longitudinal data collection of all children aged 0 – 19 years treated with nusinersen. Intrathecal injections of nusinersen were given according to the protocol. Standardized assessment with CHOP – INTEND and HFMS was performed at baseline and 420 days after the start of treatment. AE were regularly recorded. Results: Of 27 patients, 25 were followed for 420 days. Namely, 2 patients discontinued with the treatment – the first patient after 4th and the second after 5th intrathecal injections of nusinersen. Of the remaining 25 patients, 11 (44%) were boys and 14 (56%) girls. Twenty percent of patients has SMA type 1, 64% type 2 and 16 % type 3. Mean age at the start of treatment was 8.2 years (range 18.6; 0.2 – 18.8 years). Thirty-six percent (9) of all patients had invasive (2 children) or non-invasive (7 children) ventilation prior to treatment. Fourteen (56%) patients were evaluated with CHOP INTEND and 11 (44%) with HFMS. After 420 days of treatment (before 7th intrathecal injection of nusinersen) in the group of children, evaluated with CHOP INTEND, 11/14 patients (78.6%) improved by ≥ 1point(s) and 3/14
(21.4%) children achieved the same score. No regression of motor–milestone response was observed in the group of children, evaluated with CHOP INTEND. In the group of children, evaluated with HFMS, 5/11 (45.5%) improved by ≥ 1 point(s), in 2/11 (18.2%) there was no change and 4/11 (36.4%) children achieved less scores on the scale than before treatment initiation. Reported AE were post puncture headache and pain at the site of lumbar puncture. In 3 patients cerebrospinal fluid leakage was detected but it resolved spontaneously. Conclusion: We did not observe disease progression in the majority (21/25 - 84%) of children one year after start of treatment with nusinersen. No serious AE were observed. Further studies are needed to evaluate the long-term efficacy and side effects of nusinersen.

**Charcot Marie Tooth and Distal Spinal Muscular Atrophy**

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Background: Charcot-Marie-Tooth disease (CMT) is a heterogeneous group of hereditary motor and sensory neuropathies (HSMN). Prevalence of CMT in the Belgrade population was 9.0/100,000 (Mladenovic et al, 2010). The most frequent type was CMT1 followed by CMT2. Prevalence of CMT2 was 2.0/100,000. Distal spinal muscular atrophy (SMA) is motor neuronopathies, clinically very similar or identical with neuropathies (Bansagi B et al, 2016). Aim: Clinical and genetic analysis of Serbian CMT and distal SMA. Method: The diagnosis of CMT was established at Clinic of Neurology and Psychiatry for Children and Youth, Belgrade. Conventional techniques was applied for EMNG studies. Molecular genetics studies were done in the Center for human molecular genetics, Belgrade and VIB Department of Molecular Genetics, Antwerpen. Results: Autosomal dominant (AD) demyelinatig HSMN is most frequent, especially CMT1A, due to 17p11.2 duplication. X-linked neuropathy with GJB1 mutations are the second most common cause of CMT with most frequent c.94A>G mutation, which was defined as founder type (Keckarevic et al, 2009). Within
rare autosomal recessive (AR) CMT2 we found also founder (c.110G>C) mutation in HINT1 gene (Zimon M et al, 2012) for Serbian patients. Our genetic results influence on our algorithm approach to hereditary neuropathy in childhood (Keckarevic M et al, 2012). Distal SMA may be phenotypically identical to CMT. Further possible progression of distal SMA may present differential diagnostic problem with proximal SMA. Conclusion: We will present the most frequent CMT in Serbian patients and we will discuss about distal SMA between CMT and proximal SMA.

Treatment Possibilities in Progressed DMD

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Duchenne muscular dystrophy (DMD) is a severe, progressive rare genetic X-linked childhood muscle wasting disease that primarily affects boys and is characterized by relentless decline in function. Absence of dystrophin in DMD leads to muscle degeneration and fibrosis; DMD has also a progressive impact on multiple organ systems. Goals of DMD treatment are to stabilise muscle destruction and prolong walking ability, delaying critical disease progression milestones. Earlier loss of ambulation predicts a faster deterioration of key milestones in patients with DMD, such as time to ventilation. Respiratory failure is the most common cause of death in DMD patients, and assessment of respiratory function is an important outcome in DMD patients. Until recently, DMD standard treatment was palliative, aimed at alleviating symptoms and managing complications. The drug development pipeline for DMD has changed dramatically since the publication of the 2010 care considerations, and the full list of DMD treatment trials changes continually. In recent years, coordinated multidisciplinary management of DMD has improved the quality of care, with early corticosteroid use prolonging independent ambulation, and the routine use of non-invasive ventilation significantly increasing survival. Ataluren and eteplirsen are the first of a series of mutation-specific therapies to gain regulatory approval: as of 2014, ataluren was granted conditional marketing authorisation in EU, targeting boys with DMD caused
by a nonsense premature stop codon in the dystrophin gene. In September, 2016, FDA approved use of eteplirsen, which targets the boys with a mutation in the dystrophin gene that is amenable to exon 51 skipping. Further research is needed into a better understanding of predictive measures of respiratory system dysfunction and what the optimal time is to initiate clinical support therapies. The next target to improve outcomes is optimising treatments to delay the onset or slow the progression of cardiac involvement and so prolong survival further.

All You Need to Know About a Diet of Children with Autism Spectrum Disorder

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Autism spectrum disorders (ASD) are a group of complex pervasive developmental disorders with a neurological and biological basis, characterized by impaired social interaction and communication as well as restricted or repetitive patterns of thoughts and behaviour. In addition to neurological and behavioural symptoms, ASD children have high incidence of gastrointestinal co-morbidities including chronic constipation and diarrhoea. Several studies have shown significant changes in the composition of the gut microbiota in children with ASD and have suggested that microbiota could play an important role in one's health. Accumulating evidence has shown a link between alterations in the composition of the gut microbiota and both gastrointestinal and neurobehavioural symptoms in children with ASD. Diet is one of the most effective factors influencing intestinal microbiota. Therefore, there are some suggestions that diet manipulation could help alleviate the disease severity, as well as the psychological and gastrointestinal symptoms. In the past few decades, research on how nutrition and diet affects autism has been increasing. Particular attention has focused on elimination diets like gluten free and casein free diet, exclusion of food additives and refined sugar, ketogenic diet, etc. However, most of the evidence has found them to be inconclusive. The most important aspect of nutrition in children with ASD is firstly to ensure adequate nutritional status.
due to their selective eating behaviour. Furthermore, the diet should be individually adapted to the patient’s needs preventing possible nutritional deficiencies. Consequently, it is important to include a professional dietitian as part of routine healthcare for all individuals with ASD. With the current knowledge, it is not yet possible to develop a gut microbiota-based nutritional intervention to treat symptoms associated with the ASD, hence further research is needed.

Neurofibromatosis – an Epidemiological Overview and Therapeutic Algorithm

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Neurofibromatosis type 1 (NF 1) is a genetic multisystem disease, primarily affecting cell growth of neural tissues, leading to tumors, which can appear at virtually any location and at any time. Approximately 1 in 3000 to 4000 individuals is affected, making it one of the most common inherited diseases. The diagnostic criteria for the disease are very well defined, therapeutic algorithms less so. Currently 146 patients with possible NF 1 are being followed at our clinical center. Of these 92 (63%) fulfill the clinical or genetic criteria for the diagnosis, the rest are patients who currently display isolated café-au-lait stains. The phenotype of the disease varies greatly and severe phenotypes are rare in our population of patients. So far, only six patients have needed therapeutic interventions, such as surgery or chemotherapy. We have to take into consideration though, that possibly not all Slovenian NF 1 pediatric patients are referred to our center and thus the phenotype variability might be even greater. We can say, though, that close clinical follow-up, especially in the pediatric population and a multidisciplinary approach are mandatory for the optimal outcome in these patients. Defining a solid diagnostic and therapeutic algorithm for Slovenian pediatric NF 1 patients, adhering to the basic international guidelines, and raising awareness of the disease, especially in the population of referring pediatricians, should further ensure all patients receive optimal management of their disease.
Neurological Manifestations of Mitochondrial Disorders

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Mitochondrial diseases encompass a spectrum of genetically determined disorders characterized with disturbed function of mitochondria. These organelles have a central role in intermediary metabolism. Defects of oxidative phosphorylation are considered synonymous with mitochondriopathies, but today this spectrum includes deficiency of pyruvate dehydrogenase complex and Krebs cycle disorders as well. Joint prevalence of mitochondriopathies could be estimated at 5-15:100,000 live births. The hallmark of these disorders is wide clinical heterogeneity. Accordingly, clinical manifestations can arise at any age, and practically all organs and systems can be affected by the pathologic process. However, tissues highly dependent on energy supply are the most severely changed in patients: brain, muscles (including heart), kidney, liver, intestinum, bone marrow, endocrine glands etc. There are certain, well-defined patterns of mitochondrial disease, recognized as clinical syndromes, such as Leigh syndrome, MELAS, MERRF, Pearson syndrome, Alpers-Huttenlocher syndrome and others. On other hand, early onset in infancy with severe hypotonia, lactic acidosis, seizures and failure to thrive is usually associated with mutations in nuclear genes important for mitochondrial function and structure. Most common neurologic signs are: hypotonia, ataxia, seizures, ptosis, muscule weakness. Significant advances in genetic diagnostics over the past decade, especially the introduction of next generation sequencing in clinical practice, provided the possibility of distinguishing rare mitochondrial entities. Today, it is possible to elucidate genetic basis of the mitochondrial disease in around 60% patients which is multifold higher than only several years ago. Treatment of these disorders is based on the combination of vitamins, cofactors, alcalizing agents, symptomatic and supportive measures. We will present some of the patients in whome we made diagnosis of mitochondrial disease.
Clinical Characteristics of Slovene Children with Multiple Sclerosis

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Background: Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) characterized by demyelinating lesions of the CNS, which cause focal neurological symptoms and signs disseminated in time and space. Although multiple sclerosis usually affects young adults, paediatric-onset multiple sclerosis (pMS) is increasingly recognized in the past ten years. Pediatric MS patients reach a comparable degree of disability 10 years earlier than patients with adult-onset of the disease. Therefore, early diagnosis and recognition of particular clinical characteristics associated with pMS is of importance for long-term management and patient well-being. Purpose: The aim of the present study was to evaluate the incidence of pMS in Slovenia and to characterize the clinical, laboratory and neuroradiological characteristics of pMS at the disease onset. Methods: We performed a national retrospective descriptive study including all patients diagnosed with pMS between January 1992 and June 2017. We reviewed data of all patients younger than 18 years at the first demyelinating event. Case records were reviewed for gender, age at first symptoms of pMS, time to diagnosis, symptoms at onset, disease course at presentation (relapsing-remitting or progressive), family history of MS, associated secondary disease, cerebrospinal fluid (CSF) findings, magnetic resonance imaging (MRI) findings at the first demyelinating event and data about prescribed treatments. We have subdivided the patients into two age groups, the childhood-onset group (12 years or younger) and the adolescent-onset group (older than 12 years). Results: The estimated incidence of pMS was 0.66/100,000 children per year. We included 61 patients (77% were female) with a median age at diagnosis of 16.3 years. In 4 patients, onset of pMS was before the age of 12 years old (childhood-onset pMS). Relapsing-remitting multiple sclerosis was most prevalent, with only 2 patients presenting a primary progressive pMS. Polysymptomatic pMS was
found at onset in 59% of patients and monosymptomatic in 41%. All patients in the childhood-onset group presented with polysymptomatic manifestation. Only 2 patients were initially diagnosed with acute disseminated encephalomyelitis (ADEM). In the cerebrospinal fluid study, 88% of patients had positive oligoclonal bands. Brain magnetic resonance imaging studies showed a predominant supratentorial involvement (100% of patients). Seventy percent of patients were treated with high dose corticosteroids at first relapse. Forty-six patients (75%) had received immunomodulatory therapy at some point during their disease. Conclusion: The clinical pattern of pMS in our cohort of patients was characterized by polysymptomatic presentation and predominantly sensory symptoms at onset, developing a relapsing-remitting pMS pattern. These results may help increase awareness of pMS symptoms and age dependent risk for MS, subsequently leading to an early and correct diagnosis of pMS and early start of adequate treatment.

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**Immune-Mediated Cerebellar Ataxias in Children**

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Among a vast number of conditions that affect cerebellar function in children of particular importance are immune-mediated acute and subacute ataxias. They may differ from similar disorders in adults although the immune-mediated damage to the cerebellum could be the same. The most often target of insult are Purkinje cells, the most common trigger is an infection/vaccination and the most common clinical presentation is ataxia. The focus will evolve pathophysiology of cerebellar autoimmunity, clinical and diagnostic algorithm, differential diagnosis, specific entities ie. OMAS, quantitative rating scales used to follow the natural progression of disease and response to therapy. Treatment usually includes immune-modulating therapies, but no clear consensus is established due to rarity. However, treatment, if needed, should be initiated at an early stage to prevent recurrences and neurological sequelae.
Prevalence and Genetic Subtypes of Congenital Myasthenic Syndromes in the Pediatric Population of Slovenia

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Introduction: Congenital myasthenic syndromes (CMS) are rare, genetically and phenotypically diverse genetic disorders of neuromuscular transmission. Data on prevalence among children are scarce with just a few studies conducted in specific countries. The clinical spectrum is varied, depending on the type of mutant protein. Whole exome sequencing facilitated discovery of novel CMS mutations and to date over 30 genes have been implicated. Treatment varies depending on the CMS genetic subtype. Our aim was to identify the prevalence, genetic subtypes and clinical characteristics of CMS in pediatric population of Slovenia.

Methods: Medical records were retrospectively reviewed for all patients with CMS, referred over a 19-year period (2000-2018) to the Department of Child, Adolescent and Developmental Neurology, University Medical Centre, Ljubljana, Slovenia. All patients with genetically confirmed CMS were included in the study. Genetic and phenotypic characteristics of CMS were collected for all patients and prevalence of CMS in children was calculated. Results: Eight children (3 males, 5 females) with a confirmed genetic diagnosis of CMS from 6 unrelated families were included. Based on the genetic subtypes, 4 patients (50%) had a primary acetylcholine receptor (AChR) deficiency caused by a mutation in one of the subunit genes (3 CHRNE and 1 CHRND), 3 (37%) patients had a defect in the end-plate potential development and maintenance caused by a RAPSN or MUSK mutation and 1 (12,5%) had a choline acetyltransferase (ChAT) deficiency due to a mutation in the CHAT gene. Calculated prevalence of genetically confirmed CMS in Slovenian children was 22.2 cases per 1,000,000 children. Conclusion:
The prevalence of genetically confirmed CMS in Slovenian children at the end of 2018 exceeds previously reported prevalence by more than two-fold, which suggests that CMS is often a missed diagnosis and the previously reported prevalence in the literature is likely to be underestimated. As expected genetic subtypes of CMS in Slovenia are diverse, with similar distribution as elsewhere in Europe, since half of the CMS patients are diagnosed with AChR mutations. On the contrary, two seldom reported genes were causative for CMS in two of eight patients, namely CHRND and MUSK mutations.

Slovene Cohort of Patients with Farmacoresistant Epilepsy Treated with Cannabidiol

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The interest of researchers, the pharmaceutical industry and especially clinicians for treatment with cannabinoids (especially cannabidiol – CBD) and natural cannabis products has increased enormously during the past decade. After first, more or less, anecdotal reports about the benefits of these substances for use in children with resistant epilepsies and some other severe neurological conditions, few open-label studies appeared on a small number of such children, confirming the efficacy of cannabidiol and other cannabis products (Devinsky et al., 2016; Tzadok et al., 2016). Today multicentre and randomised, double blind, placebo-controlled trials confirmed these facts (Devinsky, Marsh et al., 2016; Devinsky et al., 2017; Thiele et al., 2018). In our own study (Neubauer et al., 2018) from a single tertiary centre in Slovenia we have also seen excellent results (using only pure CBD), as out of 66 children with severe epilepsies and even encephalopathies, thirty-two (48.5%) patients had a more than 50% improvement regarding seizure burden, 14 of whom (21.2%) became seizure-free. None of the patients reported a worsening of seizure frequency, and adverse effects were very mild and reported in only 5 of 66 children. Recently the first cannabis-derived medication got approval from the US Food and
Drug Administration (FDA) and waiting for approval from European Medicines Agency (EMA). This CBD formulation significantly reduces seizures as an adjunct to standard antiepileptic therapies in patients ≥2 years old with severe epilepsy syndromes (Devinsky et al., 2019). We have recently studied also a small group of children with severe epileptic encephalopathies where parents decided to treat them with a natural cannabis product (or medicinal grade cannabis – MGC, which also contains certain amounts of delta-9-tetrahydrocannabinol - THC ) and we also proved, like some others (Porcari et al, 2018; Pamplona et al, 2018), that also such MGC products are very efficient for these severe conditions, while the side-effects (even with higher concentrations of THC) are minor.

Practical Experiences and Perceptions of the Effects of Kanobil® Epi as an Additional Treatment in Refractory Epilepsy in Children

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Epilepsy, defined as recurrent unprovoked seizures, occurs in 1–2% of the pediatric population. Up to 40% of children with epilepsy will not achieve seizure freedom with antiepileptic drugs (AEDs) Cannabis-based treatments for epilepsy have generated much interest, and clinical use of cannabis based products in the treatment of epilepsy is one of most scientifically researched. Purpose: To describe the experiences and perceptions of the effects of available medical cannabis as prescription drug containing 1800 mg cannabidiol (CB) and 120 mg tetrahydrocannabinol (THC) (CB-THC) as additional treatment in refractory epilepsy in 20 children.

Methods: A prospective observation describing the effect of CB-THC as additional treatment in 20 outpatient children (age range 3 –11 years) with intractable epilepsy resistant to >2 antiepileptic drugs and signed informed consent from the parent/responsible person in period July 2017- May 2018. CB and THC, oil solution for oral use (oil extract from cannabis for medical use), containing 15 mg CBD and 1 mg THC/ 1 ml was
used as additional treatment for a period of six weeks with titration scheme of gradually dosing in accordance with Patient information leaflet. Observation was conducted by following: efficacy of the treatment as measured by number and frequency of seizures and tolerability as measured by frequency of appearance and strength of undesirable effects. Efficacy and tolerability were assessed by parental diary report. Results: Effects of treatment with CB-THC were assessed in 17 children, due to lack of feedback information from parental diary. Treatment with CB-THC generally yielded positive effect on seizure load. One patient was seizure free. Reduction in seizure frequency ranging (50-80%) was reported for five (~29%) patients, intermittent reduction of seizure frequency was reported for four children (~24%) and for three children (~18%) insignificant change in seizure frequency was reported. Five (~29%) patients withdraw the treatment: two due to no adherence to treatment, one due to operation procedure and in two patient aggravations of seizures were reported. For 12 patients with different range of seizure reduction, all parents reported improvement in behavior and alertness, communication and mood, appetite and sleep. No adverse reactions were reported. Conclusion: The results of this observation on CB-THC treatment for intractable epilepsy in children are promising and further prospective trials with larger and more homogenous group of patients are warranted. Limitation to the observation: small group of patient, heterogeneous basic diagnosis and symptoms, adherence to treatment, results reported as perceived by parents.

Case #1: A Girl with an Atypical Form of Dravet Syndrome

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Epilepsy in females with mental retardation (EFMR) is included in a phenotypic spectrum of Dravet syndrome (DS), which is a genetically heterogeneous condition. 20 to 30 percent of patients with DS do not have identifiable mutations in SCN1A gene. Protocadherin-19 (PCDH19) mutations, found in EFMR, account for approximately 5 percent of all patients with DS. The EFMR patient’s onset of
seizures, which are febrile seizures in half of the cases, usually occurs in infancy or early childhood. Seizures are typically induced or worsened by high temperature. The frequency of seizures decreases with the patient’s age. Mental retardation, ranging from mild to profound, develops in patients who appeared to be normal prior to the onset of seizures. The PCDH19 gene is located in locus Xq22.1. The majority of the PCDH19 mutations arise de novo, but around 30% of the EFMR cases are passed in families with a unique pattern of inheritance. Unlike in other X-linked diseases, hemizygous males carrying the PCDH19 mutation remain spared, whereas heterozygous females are affected. The clinical spectrum associated with PCDH19 mutations overlaps with the more common DS caused by a mutation in the SCN1A gene, but some differences can be noted. EFMR females have a later mean age of seizure onset, 14 months versus 6 months in SCN1A cases. They usually have a lesser degree of intellectual disability than that observed in classic DS. Photosensitivity, atypical absence and myoclonic seizures are also less frequent in EFMR patients. Whereas status epilepticus is a common feature of DS, in EFMR seizures are not long in duration, but they typically occur in prolonged clusters. We present the story of our patient with EFMR epilepsy and her way to the precise diagnosis. PCDH19 gene analysis should be performed in every Dravet-like SCN1A-negative female, where it may contribute to around 25% of cases, which makes it the second (after SCN1A) most clinically relevant gene in epilepsy.

Case #2: Idiopathic (benign) Intracranial Hypertension – Is It Really a Benign Condition?


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INTRODUCTION: Idiopathic (benign) intracranial hypertension (IIH) or pseudotumor cerebri is disorder characterized by increased intracranial pressure, without any obvious underlying cause. Most common symptoms are headache and vomiting, most
prominent sign is n. abducens palsy, while fundoscopy reveals papilledema. Treatment is usually conservative, but in serious cases surgical intervention is required, mostly in form of shunting. METHODS: We present a patient in whom IIH occurred after upper respiratory tract infection with mastoiditis that led to compression of cavernous sinus. Despite polyvalent medicamentous treatment and repeated lumbar punctures, patient had to undergo lumbo-peritoneal (LP) shunting which led to complete remission of symptoms. Two years later control MRI showed development of pseudo-Chiary, protrusion of cerebellar tonsils for 25 mm, which was interpreted as sign of shunt hyperfunction. Patient underwent decompression of posterior fossa, which gave short relief, but soon after uncal herniation appeared, while LP shunt was no longer visible. At that moment patient was in life threatening condition, with high intracranial pressure, severe papilledema and retinal bleeding. Finally, ventriculoperitoneal (VP) shunting was performed, but after initial regression of symptoms, headaches and nausea reoccurred. MRI of LS region showed pseudomeningocele at place of former LP shunt. Since last procedure of LS dural plastic, patient is without any symptom for three years now. CONCLUSIONS: Headache is very common symptom, but also can be a sign of life threatening condition of increased intracranial pressure. Targeted neuroradiological examination is important in diagnostic of IIH, and if disorder does not resolve on conservative treatment, surgical intervention is mandatory, despite all possible complications.

Case #4: Rare Mutation of Congenital Myasthenic Syndrome

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Congenital myasthenic syndromes are group of neuromuscular junction disorders. The most common classification of CMS relies on the location of the mutated protein, in presynaptic, synaptic basal lamina or postsynaptic components of the neuromuscular junction. Prevalence of genetically confirmed cases is approximately 9,2 per million. The syndromes share some of the clinical features...
like fatigable weakness but are heterogeneous considering age of onset, distribution of weakness, response to therapy because of the underlying genetic defect. We are presenting a boy, age 14, with generalized fatigable weakness that worsens during the day and has become more prominent for the past 2 years. He was born from uneventful pregnancy but presented in infancy with feeding difficulties, hypotonia and prolonged, recurrent respiratory infections. He started walking at the age of 18 months and developed a slurred speech that needed a logopedic therapy. He had eyelid ptosis since birth. Because of the scoliosis he went to psychiatric examination and was referred to neuropediatrics. His laboratory findings including CK and antibodies against AchR i MUSK were normal, but EMNG findings considering repetitive stimulation was positive. He was referred to genetic testing – Neuromuscular Disorders Panel. We got positive result – pathogenic variant identified in CHRD gene responsible for CHRND protein function. Up to date, 32 gene mutations are reported in CMS, CHRND represented in 1% of all mutations so far. CHRND protein is one of five subunits of acetilcholin receptor and by that a mutation of CHRND gene is responsible for AchR malfunction but can also affect the kinetics of AchR leading to prolonged (slow channel syndrome, SCS) or brief openings (fast channel syndrome, FCS). Our patient had clinical features that mostly resembled SCS phenotype, but had his first symptoms in infancy which is not the case in SCS. On the basis of described cases so far, patients can be treated with 3,4-DAP and pyridostigmin, but if our patient had SCS there could be a deterioration of clinical manifestations if treated with pyridostigmin. Because of that, we have done a pyridostgmin test that was positive and he started the therapy with pyridostigmin.

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Case #6: Opsoclonus-Myoclonus Syndrome - Case Report

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Opsoclonus myoclonus syndrome is defined by opsoclonus, myoclonus, and ataxia, behavioral and sleep problems. Mostly, it is
paraneoplastic associated with different kind of cancers, in children mostly with neuroblastic tumors. Case Report: We report the case of a 2-year-old girl who developed an ataxia without a known trigger. Hospital submission was necessary by persistent ataxia and suspected encephalitis. Different diagnostic tools (CCT, cMRI, lumbal puncture, search for auto antibodies, and virological diagnostic) showed normal results. The next days, the girl besides the ataxia showed muscular hypotonia, tremor, sleep and behavioral problems, and some strange ocular movements but not real opsoclonus. A neuroblastic tumor could not be found. Under therapy with dexamethasone (pulse, 20 mg/m2) which resulted in a good neurologic improvement. During the first three cycles, there was always a short worsening with recurrence of the ataxia, sleep disturbance and behavioral problems directly before dexamethasone was given. Meanwhile there is a constant improvement. We show videos from the first signs of opsoclonus myoclonus sy directly after first corticosteroid treatment up to the current state after 3 months.
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