VIDEO ABSTRACTS

Epilepsy, dyskinesia and ASD in an infant with probably ALG1 mutation (CDG-Ik) – a case presentation

Mihaela Adela Vintan [1], Camelia Al-Khzouz [1], Diana Miclea [1]

University of Medicine and Pharmacy - Cluj Napoca (Romania)

Introduction: Epilepsy associated with ASD is a group of highly heterogeneous diseases with various phenotypes. Their genotype has recently started to be studied. SCN1A and MECP2 are responsible for most of the phenotypes. Voltage-gated ion channel activity genes played an important role in epilepsy with ASD patients, including SCN1A, SCN2A, CACNA1A, CACNA1H, CACNA1D, and KCNQ2. Still, in 50% of these children, the etiology remains unknown, yet.

Methods: We present a boy, from a non-consanguineous family, a healthy older brother; with uneventful pregnancy and birth. He had normal development in the first 3 months of life. From the fourth month, he started to present seizures, with focal onset, tonic, with impaired awareness and epileptic spasms, rare but associated in time, with microcephaly and cognitive and motor deterioration with autistic features. Hepatic cytolysis was associated from early infancy. Around the age of 1 year he developed dyskinesia. Seizures became resistant to therapy and the development was slow, both motor and cognitive.

Results: The etiology was investigated. MRI was normal. Congenital infections were excluded (TORCH). Due to the fact that there were signs pointing on a metabolic disorder, aminoacidopathies and organic acidurias, acylcarnitine profile, lysosomal disorders, very long chain fatty acids, copper metabolism were evaluated and revealed normal values. MLPA (SALSA MLPA KIT P245 Microdeletion syndromes, MRC-Holland) was performed and showed negative results. More extensive genetic panel for neurometabolic disorders was performed and showed one pathogenic variant identified in HEXA,. Variants of Uncertain Significance (US) identified in ALG1, SLC22A5 and ST3GAL5. No symptoms or signs or symptoms of Tay-Sachs disease were identified, but characteristics of ALG1 mutation were more probable pointing to an autosomal recessive ALG1-congenital disorder of glycosylation (CDG-Ik)

Conclusions: What did we do wrong? The extensive genetic panel in our case, revealed a pathogenic mutation apparently not related to clinical picture or it is a particular variant of Tay-Sachs disease or an US variants identified could play a more important role?

Co-occurence of epilepsy and paroxysmal dyskinesia - case report

Galina Stevanovic [1], Vesna Brankovic [1]

Clinic Of Neurology And Psychiatry For Children And Youth - Belgrade (Serbia)

Introduction: Co-occurrence of epilepsy and paroxysmal dyskinesia has a genetic background. Pathogenic mutation, for example in PRRT2 or SLC2A1 gene, by different mechanisms, could result in disruption of neurotransmitter release regulation and thus impair neurotransmission. On the other hand, channelopathies (KCNMA1, SCN8A, SCN1A etc), due to gain or loss-of-function mutations, lead to neuronal hyperexcitability disorders. Mutations in ADYC5 or ATP1A3 gene could be connected with the similar phenotype.

Methods: The 11-year-old patient was diagnosed clinically with infantile epilepsy and paroxysmal dyskinesia. Electrophysological studies and MRI of the brain supported the diagnosis. Genetic analyses using NGS ended without well-known causative pathogenic variant.

Results: The patient was born as the first child from an uncomplicated pregnancy and delivery. Psychomotor development was normal. At the age of 8 months he presented with the first bilateral tonic clonic seizure, followed by focal seizures and paroxysmal dyskinesias. Short-term bilateral choraoathetoses with orofacial dyskinesia were induced by sudden movement or emotional stress. Introduction of sodium channel blockers (high dose of carbamazepine) reduced seizure frequency and dyskinetic episodes, by the age of 3. After two years, at the age of 5, seizure frequency gradually raised coupled with EEG aggravation- almost continuous right temporal spike-wave discharges during wake and sleep were present from the age of 7. Repeated MRIs at the age of 2 and 8 respectively, were normal. On evolution, sensations described by the boy as “stones” in his right fist or right hamstring, were followed by bilateral tonic clonic seizures. By normal EMNG findings, suspicion of myotonia was ruled out. Reaching puberty seizure semiology has been changed, becoming more frequent and more complex with evolution to bilateral motor status epilepticus. NGS revealed various mutations, some of them as pathogenic (PHGDH, PCCB and CYP21A2), but, to our knowledge, they do not correlate with the phenotype.

Conclusions: A boy with co-occurrence of pharmacoresistant epilepsy and paroxysmal dyskinesia has been presented, without defined genetic background so far. Although current treatment options are symptomatic and empiric, we assume that revealing possible genetic pathology and gene-phenotype correlation, could lead us better understanding pathophysiology and treatment strategies.

NCAM2 deletion in a boy with neurodevelopmental disorder, epilepsy and subtle movement disorder

Dina Amrom [1], Jean-Hubert Caberg [2]

[1]Centre Hospitalier De Luxembourg - Luxembourg (Luxembourg), [2]Centre Hospitalier Universitaire De Liège - Lège (Belgium)

Introduction: Neural Cell Adhesion Molecule (NCAM2) proteins are involved in axonal migration, synaptic formation and plasticity. *NCAM2* deletion has been associated with neurodevelopmental disorders and has been proposed as a candidate gene for autism. To our knowledge, *NCAM2* has not been associated yet to epilepsy and/or movement disorders.

Methods: Clinical report on the epilepsy and movement disorders observed in a patient harboring a 21q21 deletion involving *NCAM2* gene.

Results: A 5-year-old boy was evaluated because of onset of generalized seizures at 15 months of age.

The patient was eumorphic, he was noted to have axial hypotonia, global developmental delay, absent verbal speech, some autistic features, and subtle non paroxysmal dyskinesia of the trunk and limbs. Electroencephalogram showed a moderately slowed background activity. Brain magnetic resonance imaging was normal. Molecular karyotype showed a *de novo* deletion of 308.9 kb in the 21q21.1 region, involving several exons of *NCAM*2, considered as a variant of unknown significance. Next generation sequencing in trio of a gene panel for 3989 rare diseases (mendeliome) came back negative. The treatment with valproic acid and lamotrigine is quite effective in controlling the seizures.

Conclusion: We provide a comprehensive clinical and molecular characterization of a patient harboring a 21q21.1 deletion involving *NCAM2.* We hypothesize that our patient's abnormal phenotype may have resulted from a loss of function of NCAM2, and if so, the present report extends the phenotype of this neurodevelopmental disorder.

Epilepsy and hyperkinetic movement disorders in a patient with Williams-Beuren syndrome

Mario Mastrangelo [1], Laura Giordo [1], Maria Teresa Giannini [1], Flavia Giannotti [1], Vincenzo Leuzzi [1]

Sapienza University Of Rome - Rome (Italy)

INTRODUCTION: Williams-Beuren syndrome (WBS; OMIM 194050) is a genetic disorder characterized by typical facial dysmorphisms, aortic stenosis, weakness of connective tissue and short stature. Classical neurological involvement include mild-to-moderate intellectual disability, motor impairment and a characteristic behavioral profile with talkative personality.

METHODS: Reported here is an 18-month-old child with developmental delay, epileptic seizures and hyperkinetic movement disorders.

RESULTS: His familial history was unremarkable. He received a pre-natal diagnosis of aortic and pulmonary stenosis with a subsequent post-natal follow-up in a pediatric cardiologic setting.He was referred to our institution at the age of 18 months because of a developmental delay (he had achieved the trunk control but not the following motor milestones and language was limited to vocalizations), tonic and atonic epileptic seizures, and hyperkinetic movement disorders (choreiform movements of the limbs and subcontinous oscillatory stereotypes involving trunk. Head and limbs). Suggestive facial dysmorphisms (including epicanthal folds, iris stellata, a short nose with flat nasal bridge and broad tip, prominent upper and thin lower lip, small and widely spaced teeth and delicate chin) were evidenced. Ictal video-EEG evidenced diffuse spikes, sharp waves and spike and waves and a remarkable voltage decrease during an episode of atonic head drop associated with a tonic extension of the upper limbs. Brain MRI was normal. FISH evidenced the del (7)(q11.23q11.23)(ELN-) and confirmed the diagnostic suspect of WBS. Seizures were controlled with the association of valproate and clonazepam.

CONCLUSIONS: The present case illustrates that WBS should be included in the genetic syndromes including an epilepsy-dyskinesia spectrum.

Epilepsy is relatively infrequent in WBS with less than 30 cases being reported in the literature, a variable semiology (mainly infantile spasms, but also focal motor seizures, myoclonic seizures, tonic and atonic seizures) and a good response to antiepileptic therapies. Hyperkinetic movement disorders are not a common distinctive feature of WBS. Motor impairment in WBS may include gross and fine coordination impairments, diminished control of balance and mild extrapyramidal signs as well as gait abnormalities resembling gait hypokinesia. A probable pathogenic role was suggested for mutations of genes encoding for the transcriptional regulators belonging to the GTF family (that are located in WBS critical region on 7q11) that resulted in a decreased motor coordination in mice models.

Acyl-CoA-binding domain-containing protein 6 (ACBD6) loss of function leads to GSMDE

Rauan Kaiyrzhanov as part of ACBD6 International Collaboration

University College London, Queen Square, London, and multiple international Institutes and Centres

Introduction: Human acyl-CoA-binding domain-containing protein 6 (ACBD6) is a member of ACBD protein family with diverse cellular functions including neural stem cell self-renewal, protein and lipids acylation, lipid homeostasis, intracellular vesicle trafficking, organelle formation, and apoptotic response. ACBD6 promotes the N-myristoylation of proteins, which is essential for the normal function of various human proteins (1). Here we report 15 patients from eight unrelated families with biallelic ACBD6 loss of function variants presenting with developmental delay, intellectual disability, ataxia, spasticity, and seizures.

Methods: The eight consanguineous families originating from the Middle East, South Asia, Central Asia and North Africa were identified as part of an international effort to characterize undiagnosed neurodevelopmental disorders. Exome sequencing in combination with homozygosity mapping and following Sanger segregation analysis were performed. Clinical details, neurological examination, instrumental investigations, and brain MRIs were obtained through clinical follow-up.

Results: We identified eight segregated homozygous ACBD6 loss of function variants in 15 patients. All affected individuals from eight families were the products of normal full-term pregnancy and delivery. The current age of the patients ranged from one to 37 years old. The common clinical features for all patients in our cohort were developmental delay and intellectual disability ranging from moderate to severe degree, spasticity, progressive spastic-ataxic gait, impaired or absent speech, broad nose with the depressed nasal bridge. Upper limb tremor was present in six patients. Complex partial, myoclonic, atonic, and generalized tonic-clonic seizures were present in six patients. The age for seizures onset varied from 2 to 35 years old. Electroencephalograms showed multifocal spike-wave complexes. Six patients expressed behavioral problems, and 13 patients had coarse faces with thin upper lip, everted lower lip, and prognathia. Four patients had premature aging and the oldest patient has started regressing in motor and cognitive function from the age of 30 years old. Microcephaly was among the variable features. While the younger patients were hyperactive in movements, the older patients gradually developed bradykinesia, dystonic head posturing with dystonic tremor, and signs of limb and truncal dystonia. Regarding speech impairment, patients tend to have preserved perceptive language, whereas expressive language was significantly affected. Brain MRI was abnormal in ten patients showing agenesis or thinning of the corpus callosum, dysmyelination and dilated lateral ventricles.

Conclusions: ACBD6 deficiency could potentially dysregulate protein N-myristoylation and lead to an autosomal recessive mendelian disease presenting with an early-onset progressive movement disorder, intellectual disability and seizures. Further functional studies might advance our knowledge of protein N-myristoylation pathways involved in the development of GSMDE.

References:

1. Soupene and Kuypers (2019) ACBD6 protein controls acyl chain availability and specificity of the N-myristoylation modification of proteins. J Lipid Res. 60(3):624-635.

Long-term follow-up of two siblings with Succinic Semialdehyde Dehydrogenase Deficiency

Mario Mastrangelo [1], Anna Commone [1], Federica Gigliotti [1], Vincenzo Leuzzi [1]

Dept. Of Human Neurosciences, Sapienza University Rome - Rome (Italy

Introduction: Succinic semialdehyde dehydrogenase (SSADH) deficiency (MIM#271980) is a rare defect of the gamma-aminobutyric acid (GABA) catabolic pathway, resulting in 4-hydroxybutyric acid (GHB) accumulation. The disorder presents in childhood with psychomotor retardation, seizures, hypotonia, and nonprogressive ataxia. Here we report a long follow-up of two affected siblings.

Methods: Case 1 is a 31 years old male who presented during childhood with autism, motor stereotypies (trunk swinging), hyperactivity, clumsiness, and hypotonia. Generalized epilepsy manifested at age 7 years, and sleep disorder (compulsive limb movements) manifested at age 10 years. Starting from age 15 years, he had a transient discomfort in the lower limbs while walking. On examination at age 16 years, he presented severe mental retardation, dysarthria, motor stereotypies (chaotic gesticulation, trunk swinging), mild dystonic postures of upper limbs, and paroxysmal exercise-induced dystonia (PED).

Case 2 was Case 1 youngest brother. He developed multifocal seizures, psychomotor delay, and hypotonia during the first months of life. Obsessive–compulsive disorder (OCD) was diagnosed when he was 6 years old. A gait abnormality was noticed at age 11 years. On examination at age 12 years, he presented macrosomia,mammary hyperplasia, extra nipple on the right, hypertelorism, thoracolumbar scoliosis, myopia, striae cutis distensae (on trunk and thigh), and hyperchromic skin spots. He was moderately mentally retarded and showed OCD, hand mannerisms, motor and vocal tics, poor gross-motor skills, clumsy gait, dystonia and PED. Epilepsy was partially pharmacologically controlled, with seizures once a month.

Results: Case 1 was the most severely affected of the two. His epilepsy was stable until the age of 26, when the frequence of the crises increased. At the age of 28 years his behavioural features worsened with increased disinhibition, aggressiveness and restlessness with poor nocturnal sleep. Several attempts have been made to control his behavioural phenotype, to no avail. He experienced another worsening of his epilepsy after an accidental fall exitating in a head trauma, with multiple crises of convulsive and non-convulsive status epilepticus per week. His gross motor abilities also deteriorated during the years. Currently, he is wheelchair-bound. His epilepsy and behaviour show a partial response to Vigabatrin and Topiramate.

Case 2 showed stability of his neurological features. His epilepsy was partially controlled with Vigabatrin and Topiramate, while the psychiatric symptoms were difficult to manage and had frequent severity fluctuations. At the age of 22, he started to have daily tonic-clonic seizures, that lasted up to 15 minutes, and his psychiatric symptoms worsened as well, with visual hallucinations, delusions and compulsions. He died that year from a respiratory failure during a status epilepticus.

Discussion: On the long term, SSADH deficiency shows a fluctuating clinical progression, with phases of stability followed by abrupt worsening of the epileptic and behavioural symptoms. Motor function tends to have a slower progression. PED is a peculiar feature of this disorder, hence a SSADH deficiency should be always ruled out in case of complex neurological phenotypes associated with PED.

Successful treatment of refractory chorea in a patient with a common gain-of-function GNAO1 variant by folinic acid

Ching Wan Lam [1], Wing Tak Cheng [2], Chun Hung Ko [2]

[1]Department of Pathology, The University of Hong Kong - Hong Kong (China), [2]Department of Paediatrics and Adolescent Medicine, Caritas Medical Centre - Hong Kong (China)

Introduction: A thirteen month old girl presented with global delay with dystonia. Her birth history was normal and her parents were nonconsanguineous. She had poor truncal tone and persistent fisting at five months. At age one she could vocalize but not yet babble. There were brief episodic lower limb spasms associated with fisting. Extraocular movements were normal. Vision and hearing were normal, and she had no history of seizure. Her elder sister, age eleven at the time, was healthy. Examination showed normal head circumference and growth parameters. There were no dysmorphic features or neurocutaneous stigmata. There was axial hypotonia with extremity hypertonia and brisk jerks. Systemic examinations were otherwise normal.Throughout the years, she remained non ambulatory. She had good head control and some voluntary arm movement. She only vocalized with no expressive speech. Oral feeding was satisfactory. There was no developmental regression.

Methods: She remained stable until age eight when there was a sudden onset of intractable generalized chorea and ballismus movement, precipitated by an apparently trivial viral febrile illness. Creatine kinase rose to 47343 IU/L with myoglobinuria. Renewed investigations, including cranial computer tomography and MRI, electrvideoooencephalography, sepsis workup, virology study, ceruloplasmin, peripheral smear, anti-streptolysin-O titre, anti-NMDAR study, CSF protein, glucose, lactate and culture, and urine organic acid assay again did not reveal any abnormalities. Neurodevelopmental disorder with involuntary movements (NEDIM; OMIM # 617493) was suspected and sequencing of the GNAO1 gene showed that the patient is heterozygous for a mutation in the GNAO1 gene, NM_020988.2:c.736G>A(p.Glu246Lys). This was not identified in the parents and elder sister, suggestive of *de novo* mutation.

Results: The movement disorder(MD) remained intractable four weeks after onset. It persisted throughout the day, and only temporarily ceased during sleep. She did not respond to empirical treatment with antibiotics, antiviral agents, immunoglobulin infusion, and pulse methylprednisolone. There was no response to levodopa and carbamazepine. Despite combination treatment with risperidone, nitrazepam, tetrabenazine and clonazepam, she required deep sedation with midazolam infusion. Neurosurgeon was consulted for consideration of deep brain stimulation (DBS) to abort the MD. Folinic acid was administered as a therapeutic trial for suspected secondary cerebral folate deficiency. Within two days there was marked reduction in MD, improvement in awareness and oromotor functions, and voluntary upper limb movements. Interestingly, pretreatment CSF 5-MTHF level was normal.

Discussion: The MD remained well controlled with folinic acid (75mg per day), low dose nitrazepam, carbamazepine and risperidone. Two mild relapses were precipitated during febrile illnesses two months after discharge, which were easily aborted by short-term sedation and transient escalation of folinic acid. In the ensuing ten months, no further relapse was observed despite intercurrent febrile illnesses. To our knowledge, this is the first reported case of successful pharmacological control to achieve long-term sustained remission of intractable MD in a patient with a common GNAO1 gain-of-function variant.

Ocular movements and other visual function in children with GNAO1 Syndrome

Domenica Immacolata Battaglia [1], Elisa Pede [1], Maria Luigia Gambardella [1], Simona Leone [2], Lorenzo Orazi [2], Ilaria Contaldo [3], Michela Quintiliani [4], Renzo Guerrini [5], Vincenzo Leuzzi [6], Daniela Ricci [7]

[1]Child Neuropsychiatry Unit, Gemelli Hospital Foundation, Irccs-Catholic University - Rome (Italy), [2]Gemelli Hospital Foundation, National Services And Rehabilitation And Research For Prevention Of Blindness And Rehabilitation Of Low Visions Patients - Rome (Italy), [3]Child Neuropsychiatry Unit,gemelli Hospital Foundation-Irccs - Rome (Italy), [4]Child Neuropsychiatry Catholic University - Rome (Italy), [5]Neuroscience Department, Children's Hospital Meyer-University - Florence (Italy), [6]Child And Neuropsychiatry Department, Sapienza University - Rome (Italy), [7]National Centre Of Services And Research For Presentino Of Blindness And Rehabilitation Of Low Vision Patients - Rome (Italy)

Background: De novo heterozygous mutations in the GNAO1 gene, encoding the Gα o subunit of G-proteins, are the cause of a severe neurodevelopmental disorder, featuring early infantile seizures, profound cognitive dysfunction and movement disorder. In children with language impairment and motor deficits the assessment of cognitive competences is a challenge. Visual function have been considered a window on brain development and proved to be the first sign of cognitive deterioration in children with other epileptic disorders, such as West Syndrome and Dravet Syndrome. The aim of this study was to define the clinical spectrum of neurovisual function in a cohort of 7 patients with de novo mutations in the GNAO1 gene.

Methods: We included in the study 7 children (4 males), main age 4.8 years, GNAO1 mutation confirmed , all with normal brain MRI, movement disorder and intellectual disability, 4 with epilepsy (1 early-onset epileptic encephalopathy, 3 with onset after 20 months of age). We permormed a neurovisual assessment including fixing, attention at distance, tracking (horizontally, vertically and for an arch), saccadic movements, visual acuity (by means of the Teller Cards), contrast sensitivity (by means of Hiding Heidi Low Contrast Sensitivity), strabismus. One child has been assessed longitudinally 8 times between 6 months and 4 years and 6 months.

Results: All but one children presented good fixation and attention at distance. All were able to track horizontally and vertically, 3/7 also for an arch. All but one presented horizontal saccades, 3/7 also vertical saccades. Visual acuity was immature in all, contrast sensitivity in 6/7, stereopsis was absent in all children, strabismus was present in 1/7. The longitudinal observation showed good fixing since 6 months and improvement by 2 years in attention at distance, tracking and saccades. No changes over time was observed in the other function.

Conclusions: The results showed 2 different trends of visual development according to the aspects assessed. Visual function more related to object-face exploration and recognition and environmental control, reliant on temporal lobe competences, appeared to be preserved and improving with age. These visual aspects allow to collect the information necessary for cognitive development. Other visual function that collect information about discrimination at distance, space and contrast, reliant on the occipital cortex, appear to be impaired at any age, with no sign of improvement. Our data suggest that in children with GNAO1 mutation it is possible to use visual abilities in order to improve communication and learning strategies

Sandhoff disease & sensory trick: when myoclonus and dystonia meet at the cortical-subcortical boundary

G. Olivieri[1], S. Pro[2], A. Capuano[2], C. Dionisi-Vici [1], F. Deodato[1].

[1]Division Of Metabolic Disease, Bambino Gesù Children's Hospital, IRCCS - Roma (Italy), [2]Department Of Neurosciences, Unit Of Neurology, Bambino Gesù Children's Hospital, IRCCS - Roma (Italy),

Introduction: Sandhoff disease is a rare and invariably fatal disorder of sphingolipid metabolism, caused by the deficiency of the lysosomal enzymes β-hexosaminidase A and B, resulting in GM2 gangliosides accumulation in neurons and peripheral tissues. The infantile-onset form is rapidly progressive. Neurological features include regression of milestones, progressive muscular hypotonia up to severe tetraparesis with spasticity signs, myoclonic reflexed jerks, macrocephaly, early blindness occasionally associated with cherry-red macular spots. Dystonia and epilepsy can easily concur. Neuroradiological findings generally consist of bilateral thalamic involvement.

Case Report: A 2.5-year-old boy with infantile Sandhoff disease started to present paroxysmal startles followed by elevation and tremor of the upper limbs. The phenomenon was both spontaneous and reflexed to acoustic and/or tactile stimuli, and despite its tendency to persist for several seconds, it can be easily interrupted by turning his head to one side. Massive and segmental jerks showed-up a few months before and concurred in the same period.

Diagnostic workout: The EEG with video-polygraphic study showed a rapidly progressive deterioration of the brain background activity and both cortical and subcortical myoclonus. Moreover, myoclonus was easily followed by dystonic phenomena, usually characterized by sustained tonic elevation of the upper limbs, with over-imposed vibratory tremor. The polygraphic trace showed how, in these last phenomena, the passive rotation of the boy's head to one side induces an abrupt interruption of the muscle tonic contraction, generally starting ipsilaterally and involving the contralateral limb as well, few seconds later. Brain MRI performed one year before did not revealed thalamic involvement.

Conclusions: Infantile Sandhoff disease is easily associated with reflexed myoclonic jerks and dystonia. Alleviating maneuvers, as sensory trick response, which is considered a supporting evidence for the diagnosis of dystonia, have been anecdotally confirmed by parent's patients and caregivers, but have been never reported in literature. Their occurrence, especially next to cortical myoclonic phenomena, is noteworthy as it emphasizes the overlap of movement disorders that takes place in the advanced stages of the disease when cortical dysfunction gives way to the overtake of subcortical phenomena.

Expanding the spectrum of Segawa syndrome: more than dopa-responsive dystonia

Sara Vila-Bedmar [1], Laura Carrera García [1], Jessica Expósito Escudero [1], Alejandra Darling [2], Angels García Cazorla [2], Andres Nascimento Osorio [2]

[1]MD - Madrid (Spain), [2]PhD - Madrid (Spain)

Introduction: Segawa syndrome or dopa-responsive dystonia was first defined as a neurological disorder of selective nigrostriatal dopamine deficiency caused by genetic defects in the dopamine synthetic pathway. However, there have been many reports of patients presenting not only with dystonia but also with a more severe clinical picture responsive to dopaminergic drugs. We present the case of two patients with a complex variety of movement disorders including ataxia, tremor and dystonia due to dominant mutations in GCH1 (GTP cyclohydrolase I) gene who experimented a substantial improvement with dopaminergic drugs.

Methods: Case report.

Results: *Patient 1.* The patient was a girl from non-consanguineous parents. She was born prematurely at 30 weeks of gestation. After a mild delay of motor development related to prematurity, at the age of 3, she presented with progressive truncal ataxia, pyramidal signs, intentional tremor, dystonic postures, marked stiffness and bradykinesia. She had no cognitive impairment. Her parents reported significant worsening during the day and improvement by sleep or rest. At the age of 5, she was not able to walk and had unstable seating. Extensive serum metabolic work-up, brain MRI and electromyogram were unremarkable. CSF levels of 5-hydroxyindolacetic, homovalinic acid and CSF/serum glucose ratio were in normal limits. Pterins in CSF were reduced including neopterin (6nmol/L, 9-55) and biopterin (7nmol/L, 10-52). Genetic testing revealed a pathogenic dominant mutation in GCH1 gene previously reported in Segawa syndrome. The patient experienced a significant improvement with dopaminergic drugs recovering ambulation after the first dose. *Patient 2.* The patient was a girl from non-consanguineous parents. She was born prematurely at 36 weeks of gestation, and she had a normal psychomotor development. At the age of 6 she presented with progressive ataxia, pyramidal signs, tremor and stiffness with fluctuation and worsening with fatigue and stress. She had intact cognitive function. Extensive serum metabolic work-up, brain and spinal cord MRI and electromyogram were unremarkable. CSF/serum glucose ratio was in normal range. CSF levels of dopamine and serotonine metabolites were reduced including 5-hydroxyindolacetic (53nmol/L, 87-366), homovalinic acid (193nmol/L, 202-596), neopterin (7nmol/L, 9-55) and biopterin (8nmol/L, 10-52). Genetic testing revealed a pathogenic mutation in GCH1 gene. The patient experienced a mild improvement with dopaminergic drugs.

Conclusions:

- Dopa-responsive dystonia due to GCH1 mutations must be suspected in patients presenting with any type of movement disorder or pyramidal signs mimicking spastic paraparesis, and marked diurnal fluctuation may be the main clinical clue towards the diagnosis.
- Normal levels of dopamine metabolites in CSF (5-hydroxyindolacetic and homovalinic acid) does not rule out the possibility of a nigrostriatal dopamine deficiency syndrome, therefore dopaminergic therapy should be tried in case of suspicion even before the genetic testing results.

Ataxia, verbal apraxia and late onset myoclonia: a long journey and a still mysterious diagnosis

David Jacquier [1], Jean-Marc Good [2], Fabienne Giuliano [2], Noelle Mercier [3], Giovanni Battista Foletti [4], Marine Jequier Gygax [5]

[1]Unit of Paediatric Neurology and Neurorehabilitation, Lausanne University Hospital (CHUV), Lausanne - Lausanne (Switzerland), [2]Service of Genetic Medicine, Lausanne University Hospital (CHUV) - Lausanne (Switzerland), [3]Epileptology Service, Neurological Hospital, Fondation Institution Lavigny - Lavigny (Switzerland), [4]Fondation Institution Lavigny - Lavigny (Switzerland), [5]Service of Autism Spectrum Disorder, Psychiatry Department, Lausanne University Hospital (CHUV) - Lausanne (Switzerland)

Introduction: Despite advanced technologies like genotyping, neuroimaging, and refined metabolic assessment, some cases with movement disorders associated with epilepsy remain unresolved. We illustrate such a case with video-tapes sequences from early childhood to adulthood.

Methods and Results: We present the history of a female patient assessed for the first time at the age of 3 years for ataxia and global developmental delay. At 4, she showed additionally verbal apraxia, atypical absences and atonic seizures. At 9, she developed myoclonic seizures with posterior theta slowing on the EEG. The seizures remained pharmaco-resistant to different anti-epileptic drugs (AED). The clinical picture worsen with progressive regression with gait apraxia, increased myoclonic jerks and intractable myoclonic seizures, and generalized tonico-clonic seizures at night. The clinical presentation at adulthood is similar to a progressive myoclonic epilepsy, responding partially to perampanel.

Karyotype, FISH analysis, CGH-array, and sequencing of UBE3A, MECP2, SLC2A1 (GLUT1 deficiency syndrome) were normal. Exome on an ataxia genes panel and an epilepsy and mental retardation-associated genes panel (including the genes extensively described in Gataullina et al DMCN 2019) was not conclusive. Brain MRIs remained normal, as metabolic assessments.

Conclusion: The clinical picture suggests a "tonic GABA-pathy profile" (Gataullina et al DMCN 2019), without clinically matching either to an Angelman syndrome (no attenuation of the myoclonia in the follow-up) or to myoclonic atonic epilepsy (tardive occurrence of myoclonic seizures after the age of 6). The diagnostic odyssey, illustrated by video-tapes sequences over 16 years, still goes on, and we hope that with the help of experts 'advices, the key will be found.

Key words: ataxia, late-onset myoclonia, Angelman syndrome, progressive myoclonic epilepsy.

Diagnostic journey of patient with paroxysmal jerks and seizures: video-presentation

Vera Fominykh [1], Ilia Komoltsev [1], Lev Brylev [1]

Bujanov Moscow City Clinical Hospital - Moscow (Russian Federation)

Introduction: Recognition of myoclonus and other paroxysmal jerks, determination of the underlying etiology and site of genesis remains challenging given that both acquired and genetically determined disorders have varied manifestations. We present the unresolved case with diagnostic journey of patient with epileptic myoclonus, seizures and other paroxysmal jerks.

Methods: Patient, male, 33 y.o., have epileptic seizures (by description) since 8 y.o. when after mild TBI short jerks in right leg and bilateral tonic-clonic seizures were developed. CBZ was without effects. At 10 y.o. he presented with short jerks in arms and body associated with TV watching. Routine EEG presented with generalized epileptic discharges, MRI was normal. VPA was added with positive effect (1 seizure per month). At 15 y.o. seizures were changed: daily sudden falls. After that panic attacks were developed.

Clonazepam was added with mild positive effect. At 19 y.o. tremor of head and neck, legs were presented.

At 26 he had 24-hours video-EEG monitoring with many paroxysmal jerks without any epileptic activity, and several episodes of falls. Due to lack of epileptic activity at EEG neurologist suggested functional disorder or hyperekplexia. Therapy with antidepressants was ineffective. After AEDs diminishing seizures frequency increased.

At 28 y.o. (admission to our hospital) he was treated with LEV 2000 mg, VPA 1500 mg, clonazepam 2 mg per day with partial positive effect. He has 1-2 bilateral tonic-clonic seizures per month, daily falls, paroxysmal jerks during the day and become totally asocial. He has panic attacks and mild cognitive decline.

We perform videoEEG monitoring detecting multiple jerks with and without epileptic activity and bilateral tonic-clonic seizure at photostimulation (video presentation). During the next 5 years he has slightly progressive disease course. AEDs are only partially effective (video presentation).

Results: The first main question is evaluation of epileptic and non-epileptic myoclonus from other paroxysmal events which can be very difficult for patients with complex problems. We can suggest profound EEG-EMG analysis for difficult cases.

The second question is diagnosis in this patient. We supposed progressive myoclonic epilepsy but the family did not perform genetic testing yet.

The third question is better diagnostic (genes, panels etc.) and treatment strategies in this patient.

Conclusion: Paroxysmal jerks and seizures can be very difficult diagnostic problem in patients with long disease course and psychological aspects. We should use genetic testing in order to perform accurate diagnosis in this case.

A girl with a de novo heterozygous mutation in NALCN gene and pyridoxine-dependent seizures and movement disorder

Ulvi Vaher [1], Eve Õiglane-Shlik [1], Hanno Roomere [1], Tiia Reimand [1]

Tartu University Hospital - Tartu (Estonia)

Introduction: De novo mutations in NALCN (Sodium Leak Channel, Non-Selective) gene (MIM 611549) cause a syndrome characterized by congenital contractures of the limbs and face, hypotonia and developmental delay – CLIFAHDD (OMIM:#616266). Chong et al. first reported the syndrome in 2015, and so far very few patients have been described, therefore data of the natural course of the syndrome and evolving of clinical problems in these patients is scarce.

Here we describe a girl with a de novo heterozygous missense mutation in NALCN gene (NM_001350748.1(NALCN):c.934C>G p.(Leu312Val)), who suffered from tonic and myoclonic paroxysmal episodes from the second day of her life.

Methods/Case report: She was born preterm (gestational age 30+1) from spontaneous delivery with the birth weight 1838 g, length 42 cm, and HC 28 cm. Apgar scores at 1'/5'/10' of life were 5/7/7 respectively. After birth, she was hospitalized in ICU due to altered consciousness, persistent breathing difficulty and hypoglycaemia. On the second day of life, she developed clinical generalized tonic and myoclonic seizures. Initially, an anti-seizure treatment with phenobarbital was started and, as seizures continued, levetiracetam was added. However, considering continuous-EEG monitoring from the 4th day of life epileptic origin was detected only in few myoclonias. Tonic posturing and most of the myoclonias and periodic tremor were characterictic to movement disorder without electrical correlation on EEG. Pyridoxine deficiency was suspected and confirmed through laboratory testing. Treatment with i/v pyridoxine was initiated and seizures and movement abnormalities subsided on the 7th day of her life. Pyridoxine was continued orally for 5 months. New generation sequencing of the 4800 probable disease causing genes (locally developed panel) was negative; mutation in ALDH7A1 gene was not detected. Chromosomal microarray was also without pathological changes. The cause of her developmental delay, dysmorphic features and thumbs arthrogryposes remained unknown until a next generation of gene panel (6700 genes) revealed the cause as a de novo heterozygous mutation in NALCN gene.

Discussion/Conclusion: To our knowledge there are no prior publications describing epilepsy in details in these patients. Just in few patients' the seizures were mentioned in the literature. Based on cEEG in our patient we could confirm epileptic origin only in some paroxysmal events. Considering the fact that the p.L312V mutation may affect the gating function of NALCN, the main clinical feature in these patients might be paroxysmal movement disorder.

Expanding the clinical phenotype associated with KCNC1 – related disorders

Patrícia Lipari Pinto [1], Mar O´callaghan [2], Andrés Nascimento Osorio [2], Carlos Ortez [2], Alia Ramírez Camacho [2], Javier Aparicio [2], Judith Armstrong [3], Delia Yubero [3], Alejandra Darling [2]

[1]Pediatric Department, Hospital de Santa Maria – Centro Hospitalar Universitário Lisboa Norte, EPE, Clínica Universitária de Pediatria, Faculdade de Medicina, Universidade de Lisboa - Lisboa (Portugal), [2]Neurology Department, Hospital Sant Joan de Déu - Barcelona (Spain) - Barcelona (Spain), [3]Medical Genetics and Molecular Service, Hospital Sant Joan de Déu - Barcelona (Spain)

Introduction: Progressive myoclonus epilepsy (PME) is a distinct group of seizure disorders characterized by gradual neurological decline with ataxia, myoclonus and seizures. Recurrent *de novo* mutations in *KCNC1* (OMIM*176258) were identified as a novel major cause of PME, designated as *myoclonus epilepsy and ataxia due to potassium channel mutation* (MEAK). Clinical features were firstly described as a homogeneous clinical presentation due to c.959G>A variant (NM_001112741.1). However new variants have been identified and clinical phenotypic data is broadening. **Objective:** Analyze different clinical phenotypes associated with *KCNC1* variants in order to better recognize, treat and reduce the diagnostic delay.

Methods: Three patients with *KCNC1* gene variants and their clinical data were analyzed.

Results: The three cases were from nonconsanguineous parents and had been born uneventfully at term. The patients were referred for neurologic counseling due to different neurological conditions. **Case 1**: 18-year-old boy was referred by age 3 months due to delayed early development and hypotonia. By age 10, he experienced absence and generalized tonic-clonic seizures and limb tremors that worsened by different triggers (cold water and fasting periods). By age 12 a regression of motor abilities appeared together with progressive ataxia. Last neurological assessment (NA) showed myoclonus, tremor, dysarthria, ataxic gait and pyramidal signs. **Case 2**: 14-year-old girl was referred when she was 15 months due to delayed motor development and upper limb tremor. Evolution showed a slow development with signs of cerebellar dysfunction including ataxic gait. By age 6, axial and facial myoclonic jerks appeared and were reported as seizures. Since age 12 myoclonus disappeared, being ataxia and intellectual disability the main features. Last NA showed mild dysarthria, choreic and myoclonic movements. **Case 3**: 13-year-old boy referred by age 3 due to pharmacoresistant multifocal epilepsy. Early development was reported as normal and by age of 3.6, he experienced tonic and atonic seizures. He had ongoing refractory seizures despite multiple antiepileptic medications with developmental regression. A vagal nerve stimulator insertion was required. By age 4, with fever, myoclonus and ataxia were noticed. Last NA showed dysarthria, dysmetria and ataxic. Brain-MRI showed progressive cerebellum atrophy in 2 cases. EEG showed abnormal and different patterns in all cases. WES revealed in patient 1: c.959G>A (p.Arg32His), reported as a cause of MEAK; in patient 2 c.1019C>T (p.Ala340Val) and patient 3 c.1663G>A (p.Ala555Thr).

Conclusions: We have described patients with *KCNC1* variants with very different phenotypes and more diverse than those described so far. Clinical clues were the myoclonic jerks together with ataxia and epilepsy. An episodic ataxia was described in one patient. WES revealed three different heterozygous variants in *KCNC1* gene, two of them absent from public databases.

Phenotipyc spectrum of POLR1C leukodystrophy.

Luisa Arrabal-Fernandez [1], Luis Javier Martínez-González [2], Susana Roldán-Aparicio [1], Maria Jose Sánchez-Pérez [3], Purificación Gutiérrez-Ríos [3]

[1]Neuropediatric Unit, Pediatric Department, Virgen de las Nieves Hospital - Granada (Spain), [2]GENYO Centre for Genomics and Oncological Research, Pfizer, University of Granada - Granada (Spain), [3]Biohealth Research Institute - Granada (Spain)

Introduction: POLR3-related leukodystrophy is a hypomyelinating leukodystrophy characterized by neurologic (cerebellar, extrapyramidal, pyramidal, and cognitive) and non-neurologic (dental, endocrine, and ocular) features. Previously, five overlapping clinical phenotypes were described and are now all recognized as part of the spectrum (4H síndrome, ADDH, TACH, LO, HCAHC) with presence of biallelic pathogenic variants in POLR3A, POLR3B, or POLR1C. We report a Spanish patient with hypomyelinating leukodystrophy associated with severe tremor and dystonia carrying a mutation in POLR1C.

Methods: We describe a Spanish girl 15 who was born at term from non-consanguineous, healthy parents. She presented at 2.5 tremor, nystagmus, dysmetria and unsteady gait, then subsequently developed progressive ataxia, dysarthria, spasticity (requiring the use of a wheelchair at the age of 5 years) and generalized dystonia and dysphagia. Cognition appeared largely spared. Nowadays she presents myopia and seizures. His dentition is normal, and there is no evidence of endocrine abnormalities. The patient's brain MRIs showed diffuse hyperintensity of the supratentorial and cerebellar white matter on the T2-weighted images. Optic radiations were spared. T1 sequence showed diffuse isointensity of the supratentorial white matter suggesting a hypomyelinating process. Furthermore, thin corpus callosum and cerebellar atrophy (progressive) were observed. Using as treatment propranolol she has improved tremor and with levetiracetam the seizures. Progressively she is worsening, accelerated in the adolescence with more dysphagia (she has gastrotomy tube) and more autonomic seizures. Electroencephalography (EEG) recording, nerve conduction velocities, amino acids and organic acids chromatography, lactacidemia, IgA, α-fetoprotein, urinary oligosaccharides and cerebrospinal fluid analysis (CSF) were normal. Auditory brainstem response and electromyography was normal. Array CGH show a deletion at short arm of the chromosome 16 (16p12.2). Her muscle fibres was normal but in the analysis of redox couples had inespecific deficits. Sequencing POLR3A and POLR3B was negative. Subsequently, analysis NGS (WES and RNA-seq) and metabolome analysis were carried out and candidate variations were evaluated and validated by qPCR and Sanger.

Results: Pathogenic mutations were found in POLR1C gene. NM_203290: exon3: cA193G; pM65V (rs141471029, mother carrier) and NM_001318876: exon8:cG836A: pR279Q (rs 191582628, father carrier). In POLR1C gene we also found an increase in mRNA expression (both in patient fibroblasts and blood).

Conclusion: Leukodystrophy due to POLR1C mutation is extremely rare (nine patients reported). The proportion of POLR3 –Related leukodystrophy atribuited to pathogenic variants in gene POLR1C is only 5%. This patient helps us to delineate the clinical and radiological spectrum of POLR1C hypomyelinating leukodystrophy. In our patient, ataxia cerebellar, tremor and dystonia were the prominent and the most severe symptoms. Although, we are still waiting to perform the "omic" data integration to have more and more robust results.

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Dyskinesia and pharmacorefractory epilepsy in a child with a homozygous PCDH12 mutation

Anne Koy [1], Daniel Bamborschke [1], Walid Fazeli [1], Sebahattin Cirak [1]

[1]University of Cologne, Faculty of Medicine and University Hospital of Cologne, Department of Pediatrics - Cologne (Germany)

Introduction*:* The number of genes causing epilepsy and movement disorders is constantly expanding. Additional clinical features such as brain malformations and dysmorphic features contribute to the broad phenotypical spectrum.

Case report*:* We report a four-year-old boy with global retardation, pharmaco-refractory epilepsy with onset of seizures at the age of 2 years, bilateral optic atrophy and myopia, central hypotonia and a dystonic movement disorder. His motor and speech development improved slowly at the age of six years when he started speaking a few words and walking independently. Semiology of epileptic seizures encompassed absences, tonic seizures of the arm, atonic "drop attacks", and generalized tonic clonic seizures with recurrent status epilepticus, triggered by febrile infections.

Results: Extensive metabolic and biochemical workup did not reveal any pathology. On subsequent MRIs of the brain a transient FLAIR-hyperintensity in both hippocampi with a streaky expansion into the left frontal lobe was first seen at the age of 3.8 years, disappearing in the follow-up MRI 12 months later. Via whole exome sequencing we discovered a novel homozygous mutation of the PCDH12 gene (c.1176G>A, p.Trp392*). The consanguineous parents are heterozygous carriers.

Discussion: PCDH12 (Protocadherin 12) is a member of the non-clustered protocadherin family of calcium-dependent cell adhesion proteins, which are involved in the regulation of brain development and function. PCDH12 promotes endothelial adhesion. Mutations in the PCDH12 gene are associated with various clinical features such as congenital microcephaly, intrauterine growth retardation, neonatal-onset epilepsy, dysplasia of the midbrain-hypothalamus-optic-tract, and movement disorders. Epilepsy can be multifocal and the movement disorder can resemble dyskinetic cerebral palsy. We expand the genetic and phenotypic spectrum of *PCDH12*-associated diseases by presenting a patient with a complex pharmacorefractory epilepsy-dyskinesia syndrome, without any malformations of the central nervous system, who shows progress in speech and motor development. As in previously reported cases our patient also harbors a homozygous truncating mutation leading to a complete loss-of-function effect.

Conclusion*:* As the spectrum of inherited epilepsy-dyskinesia syndromes is constantly expanding, this case report contributes to a further understanding of the phenotypic spectrum associated with *PCDH12* mutations. Early application of next generation sequencing enables a prompt diagnosis and prevents an exhausting and expensive diagnostic odyssey for children and their families.

Hyperkinesis associated with dystonia responds to pallidal deep brain stimulation

Warren Marks [1], Stephanie Acord [1], John Homeycutt [1], Laurie Bailey [1]

Cook Children's Medical Center - Fort Worth (United States)

Introduction: Dystonia can have both tonic and phasic components. Phasic dystonia, chorea and athetosis are all defined types of hyperkinesis. Not all movements are easily categorized. These seemingly random but often patterned, rapidly repetitive movements are important and extremely disabling in certain disorders, several of which have overlapping epileptic and non-epileptic movements. Extreme hyperkinetic events can be both disabling and dangerous. The ongoing caloric output makes malnutrition common. Long bone fractures may occur with uncontrolled movements in confined spaces such as wheelchairs and beds. In some patients with overlap syndromes of epileptic and non-epileptic movements, the hyperkinesis seems to be a time-linked precursor to epileptic events including status epilepticus. The causal relationship between the hyperkinesis and epilepsy in these disorders is not clear. Quantifying generalized hyperkinetic movements can be difficult. Controlling them can be even more problematic. The Pharmacologic interventions are often of limited effectiveness and come with substantial often dose-related side effects. These are further compounded by drug-drug interactions created by the need for polypharmacy.

Methods: All patients undergoing DBS at our institution are entered into an IRB approved database. Patients with mixed hyperkinetic movements not clearly classified as chorea, athetosis, myoclonus or phasic dystonia were identified for review.

Results: Since 2007 we have performed DBS on 127 patients with dystonia. Four patients with hyperkinetic-epilepsy overlap syndromes were identified including pontocerebelllar hypoplasia 2, GNAO-1, ataxia telangiectasia, and DRPLA. In each case the hyperkinesis responded to pallidal stimulation with caretakers reporting reduction of excess movements ranging from 60-80%. In two cases (GNAO-1, DRPLA) there was clear reduction of epilepsy concomitant with the reduced hyperkinesis documented by clinical and EEG.

Three patients with non-genetic hyperkinesis (2 CP, 1 tardive dyskinesia) also responded similarly to pallidal stimulation.

Conclusion: Pallidal DBS may reduce hyperkinesis. In some patients, this may also lead to a secondary reduction of epileptic events

ADCY5-related movement disorder with paroxysmal events-video case report from infancy to adolescence

Oliver Maier [1]

Children's Hospital of Eastern Switzerland St. Gallen, Department of child neurology - St. Gallen (Switzerland)

Introduction: ADCY5 mutations have been reported as a cause of early onset chorea with infantile to late adolescent onset. Symptoms on presentation include developmental delay, severe axial hypotonia and involuntary choreatic movements in combination with paroxysmal events.

Methods/Results: documented by videos we describe the clinical spectrum of a patient with ADCY5-related dyskinesia with severe paroxysmal events from infancy to adolescence, who significantly improved with deep brain stimulation.

Conclusions: ADCY5-related movement disorder is a distinct hyperkinetic movement disorders with paroxysmal attacks of chorea without any structural brain abnormality. A therapeutic option is deep brain stimulation (DBS).

KGD4 biallelic variants in two siblings with bilateral striatal necrosis: a new gene of Krebs cycle associated with Leigh syndrome

Serena Galosi [1], Anna Commone [1], Francesca Nardecchia [1], Carducci Claudia [2], Tartaglia Marco [3], Leuzzi Vincenzo [4]

[1]Department Of Human Neuroscience, Sapienza University - Roma (Italy), [2]Department Of Experimental Medicine, Sapienza University - Roma (Italy), [3]Genetics And Rare Diseases Research Division, Ospedale Pediatrico Bambino Gesù, Irccs - Rome (Italy), [4]Department Of Human Neuroscience, Sapienza University - Rome (Italy)

Introduction: α-ketoglutarate dehydrogenase (α-KGDH), with his three catalytic sites (E1-3), is responsible for the oxidative decarboxylation of α-ketoglutarate to succinyl-CoA in Krebs cycle. A fourth subunit, KGD4, necessary for recruiting the E3 subunit to the E1-E2 core of the enzyme complex, has been recently characterized.

DLD, encoding for the E3 subunit, is the only gene of this complex so far associated with human disease.

Ten cases with reduced α-KGDH activity without molecular diagnosis have been previously reported; their phenotype ranged from fatal neonatal lactic acidosis to a variable association of slowly progressive movement disorder, severe developmental delay, epilepsy, and bilateral striatal necrosis.

Methods: Here we report clinical, biochemical and genetic features of two brothers born from consanguineous parents with severe movement disorder, lactic acidosis, and bilateral striatal necrosis associated to homozygous variants in KGD4.

Results: These two brothers presented with early onset slowly progressive mixed dystonic-choreoathetoid quadriparesis. The older brother also suffered from myoclonic seizures and hypertrophy of the left heart ventricle. He died of sudden respiratory failure during an intercurrent infectious disease at the age of 28. The younger brother is still alive and has a severe generalized dystonia with prominent axial and cranial involvement associated with choreoathetosis. MRI revealed bilateral striatal necrosis and diffuse cerebral atrophy in both cases. Respiratory chain activity in muscle and PDH activity in fibroblasts were normal. Biochemical features included increased glutamate plus glutamine in plasma. A whole exome sequencing revealed homozygous c. 283G>T (p.Glu95*) variants in KGD4 gene. Enzymatic assay for alpha-KGD activity confirmed the reduced activity of the enzymatic complex.

Conclusion: This is the first report of α-KGDH deficiency associated with biallelic variants in KGD4.Clinical and radiological features of our patients overlapped with those of previously described patients with α-KGDH deficiency without molecular characterization. In conclusion we identified a second gene associated with α-KGDH deficiency.

The GRIA3 c.2477G>A variant causes a new and distinctive phenotype of early-onset multifocal myoclonus, generalized chorea and exaggerated startle reflex

Juliette Piard [1], Matthieu Bereau [2], Lionel Van Maldergem [1], Hongjie Yuan [3]

[1]Centre de Génétique Humaine, Université de Franche-Comté, CHU Besançon - Besançon (France), [2]Service de Neurologie, CHU Besançon - Besançon (France), [3]Center for Functional Evaluation of Rare Variants (CFERV), Emory University School of Medicine - Atlanta (United States)

Introduction: Hemizygous mutations in GRIA3, a gene encoding the GluA3 subunit of AMPA receptor, are known to be associated with neurodevelopmental disorders including intellectual disability, hypotonia, an autism spectrum disorder, sleep disturbances and epilepsy in males.

Methods: We evaluated a large Caucasian family in which segregate a singular phenotype according to an apparent X-linked mode of inheritance. Molecular analyses using next generation sequencing and in vitro functional studies using two-electrode voltage clamp recordings on Xenopus laevis oocytes and a β-lactamase reporter assay in transfected HEK293 cells were performed.

Results: In addition to mild intellectual disability, affected patients presented a tightly consistent movement disorder combining an exaggerated startle reflex with generalized chorea and multifocal myoclonus. The unreported GRIA3 missense variant c.2477G>A; p.(Gly826Asp) affecting the fourth transmembrane domain of the protein was identified in index patients and their unaffected mothers. Functional studies revealed that variant receptors show decreased current response evoked by agonist (i.e. kainic acid and glutamate) and reduced receptors expression at cell surface, arguing in favor of pathogenicity by a loss of function mechanism.

Conclusions: Taken together, our results suggest that apart from known GRIA3-related disorders, an unique apparently mutation-specific singular movement disorder does exist. We thus advocate considering GRIA3 mutations in the differential diagnosis of hyperekplexia and generalized chorea with myoclonus.

Episodic axial hyperextension – a case of GRIN2B Encephalopathy

Ralf Eberhard [1], Sarah Buerki [1], Robert Steinfeld [1]

University Children's Hospital Zurich - Zurich (Switzerland)

A 16-month-old girl was referred with seeming regression of gross motor skills. After reaching motor milestones with delay, she progressively wouldn't want to sit anymore; instead, she reflectively became opisthotonic when put to sit. Additionally, she presented with significant hyperreflexia. We show a video sequence that catches this movement of sudden axial hyperextension without loss of consciousness, resembling hyperekplexia. Exome sequencing revealed a de novo mutation in GRIN2B, coding for one of the subunits of the NMDA receptor and already associated with developmental delay, epileptic encephalopathy, and movement disorders. The girl has not suffered any obvious epileptic seizures so far, and EEG has shown very discrete pathologic activity; her clinical course over 1 year indicates that she might experience a mild type in the spectrum of GRIN2B encephalopathy. The typical episodic movement we show in our videos might help to think of the diagnosis of GRIN2B encephalopathy even in the absence of epileptic seizures.
A growing assembly of molecular and clinical data for mutations in the GRIN genes should allow for an ever more refined genotype-phenotype correlation in the spectrum of GRIN encephalopathies, helping to inform prognostic and therapeutic evaluation of these genetic disorders.

Non-paroxysmal movement disorders in patients with Alternating Hemiplegia of Childhood: “soft” and “stiff”

Eleni Panagiotakaki [1], Diane Doummar [2], Erika Nogue [3], Nicolas Nagot [3], Gaetan Lesca [4], Florence Riant [5], Sophie Nicole [6], Alexis Arzimanoglou [1], Agathe Roubertie [7], * *ahc Movement Disorder Study Group [8]

[1]Department of Paediatric Clinical Epileptology, sleep disorders and Functional Neurology, University Hospitals of Lyon; Member of the ERN EpiCARE - Lyon (France), [2]Service de Neurologie Pédiatrique, Hôpital Trousseau, APHP - Paris (France), [3]Centre d’Investigation Clinique, CHU Montpellier - Montpellier (France), [4]Hospices Civils de Lyon, Department of Medical Genetics, Centre de Biologie Est, Lyon University Hospital, Member of the ERN EpiCARE - Lyon (France), [5]Laboratoire de Génétique, Groupe hospitalier Lariboisière-Fernand Widal AP-HP - Paris (France), [6]IGF, Univ. Montpellier, CNRS, INSERM - Montpellier (France), [7]Département de Neuropédiatrie, CHU Gui de Chauliac, INSERM U 1051, Institut des Neurosciences de Montpellier - Montpellier (France), [8]Charlene Delaygue1, Marie Anne Barthez2, Marie Cécile Nassogne3, Anne Dusser4, Louis Vallée5, Thierry Billette6, Marie Bourgeois7, Christine Ioos8, Cyril Gitiaux9, Cécile Laroche10, Mathieu Milh11, Vincent Desportes12 (France)

Objective: To assess non-paroxysmal movement disorders in ATP1A3 mutation-positive patients with alternating hemiplegia of childhood.

Methods: Twenty-eight patients underwent neurological examination with particular focus on movement phenomenology by a specialist in movement disorders. Video recordings were reviewed by another movement disorders specialist, and data were correlated to patients’ characteristics.

Results: Ten patients were diagnosed with chorea, 16 with dystonia, four with myoclonus, and two with ataxia. Nine patients had more than one movement disorder and eight patients had none. The degree of movement disorder was moderate to severe in 12/28 patients. At inclusion, dystonic patients (n=16) were older (p=0.007) than non-dystonic patients. Moreover, patients (n=18) with dystonia and/or chorea had earlier disease onset (p=0.042) and a more severe neurological impairment (p=0.012), but this did not correlate with genotype. All patients presented with hypotonia, which was moderate or severe in 16/28. Patients with dystonia and/or chorea (n=18) had more pronounced hypotonia (p=0.011). Bradykinesia (n=16) was associated with an early age at assessment (p<0.01). Significant dysarthria was diagnosed in 11/25 cases. A history of acute neurological deterioration and further regression of motor function, typically after a stressful event, was reported in seven patients.

Conclusion: This is the first categorisation of movement disorders in AHC patients which may offer valuable insight into their precise characterization.

Atypical presentation of Subacute Sclerosing Panencephalitis: periodic hyperkinetic movements and EEG as key features in case of with unusual MRI

L. Pias-Peleteiro [1], C. Valera [1], V. Delgadillo [1], I. Alonso [1], V. González [1], N. Habimana Jordana [2], J. Muchart [3], M. Rebollo [3], T. Armangué [1], V. Fumadó [4], A. Garcia-Cazorla [1], A. Darling [1].

[1]Neurology Department, Sant Joan de Déu Hospital (Barcelona, Spain)[2]Palliative Care Service, Sant Joan de Déu Hospital (Barcelona, Spain)[3]Radiology Department, Sant Joan de Déu Hospital (Barcelona, Spain) [4]Infectious Diseases Department, Sant Joan de Déu Hospital (Barcelona, Spain)

Introduction: Subacute sclerosing panencephalitis (SSPE) is a progressive neurodegenerative encephalitis caused by the persistence of the measles virus in the central nervous system. Measles is not eradicated worldwide, contributing to be a major cause of childhood mortality.

Our aim is to describe a confirmed case of SSPE, with an unusual MRI, in which the EEG and movement disorder pattern were key features for the diagnosis.

Methods: Clinical, electrophysiological, biochemical and neuroimaging data were reviewed in a patient with confirmed diagnosis of SSPE.

Results: A 16 year-old boy with no previous medical personal or family history and adequate vaccination schedule is referred for abnormal movements starting at age 14, with no cognitive or behavioural impairment. Movements were initially described as daytime involuntary jerks initially involving the right hand, progressing to generalized jerks and grimacing, that lead to gait difficulties. These movements were aggravated with action or excitement. The rest of the motor, sensory, and cranial nerve examination including funduscopy was unremarkable. Initial brain MRI showed unilateral putaminal T2 hyperintensity suggesting vascular ischemia, with no white matter involvement. Cardiological assessment and extended laboratory blood testing including HIV serology were normal. VEEG showed periodic synchronized bursts of delta-wave activity correlating with predominantly axial spasms-myoclonus, providing the clue to diagnosis. CSF measles antibodies confirmed SSPE. Prior to definite diagnosis, a trial with L-Dopa was performed, showing no efficacy. Marked improvement of the involuntary movements was observed after starting carbamazepine. However, the patient showed a progressive motor and cognitive decline, with loss of gait, speech and oral feeding. Antiviral treatment with Isoprinosine did not modify the course of the disease.

Conclusions: Despite adequate measles vaccination coverage, SSPE remains as a preventable and fatal neurodegenerative condition. SSPE can present with atypical clinical and radiological findings. Putaminal involvement and clinical presentation as a complex movement disorder with myoclonic jerks or spasms preceding cognitive and behavioural abnormalities, add to the spectrum of atypical presentations of SSPE in children. Carbamazepine proves to be useful as a symptomatic treatment for the movement disorder in SSPE.