# POSTERS ABSTRACTS

## P1 - Epilepsy patients with TSC gene mutation: clinical and scalp EEG feature analysis

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**Introduction**: Tuberous Sclerosis Complex (TSC) is an autosomal dominant disease caused by mutations of TSC1 and TSC2 genes. This paper mainly analyzed the phenotype of Chinese TSC patients and the relationship between genotype and scalp EEG.

**Methods**: We collected 24 TSC inpatients with major clinical manifestations of refractory epilepsy from 2016 to 2018, including 10 males and 14 females. The age of onset is ranged from 3 days to 11 years old, with an average age of 20.9 months.

**Results**:

1. All patients underwent TSC gene testing, and 19 patients were detected with TSC gene mutation, among which 7 patients had TSC1 gene mutation, accounting for 29.1%. TSC2 gene mutation was found in 13 patients, accounting for 54.1%. 14 patients had epilepsy before the age of 1 years old, accounting for 58.3%.

2. The age of onset in patients with TSC2 gene mutation were earlier than those with TSC1 gene mutation, with more history of spasm, but there was no significant difference in intelligence and frequency of seizures.

3. The IID of TSC1 and TSC2 gene mutation are multifocal, generalized or hemispheric. The ictal onset are focal in 10 patients, among which 9(69.2%) patients with TSC2 gene mutation. The ictal onset of patients with TSC1 gene mutation are comprehensive +/- focal, multifocal, and hemispheric +/- focal.

**Conclusion**: Although a large number of studies about the relationship between genotype and phenotype have been reported,it is still unclear. The clinical manifestations of TSC2 are more severe than that of TSC1. The ictal onset of patients with TSC2 gene mutation is more focal.

# P2- A novel mutation of GRIN1 in a patient with hyperkinetic movements, infantile spasm and cortical visual impairment

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**Introduction:** Children with developmental epileptic encephalopathy usually have comorbidities such as psychiatric problems and movement disorders, which genetic underpinnings shared have been rapidly uncovered with advanced diagnostic methods. The mutations of the gene encoding glutamate receptor inotropic, N-methyl-D-aspartate, subunit 1 (*GRIN1*) result in neurodevelopmental disorder with or without hyperkinetic movements and seizures (NDHMS): developmental delay and intellectual disability in addition to hyperkinetic movements, seizures, cortical visual impairment, autistic features, mild facial dysmorphism and/or bilateral polymicrogyria are observed in the patients with *GRIN1* encephalopathy. In a delayed boy with hyperkinetic movements, infantile spasm and cortical visual impairment, we tried to find genetic etiology with whole exome sequencing (WES).

**Methods:** Clinical data were collected in this patient. WES was performed in the proband. The variants were prioritized according to our bioinformatics flow under possible inheritance patterns, referring single nucleotide polymorphisms databases including the Korean Reference Genome Database. The pathogenic or likely pathogenic variants found in the proband were verified with Sanger sequencing in trio samples.

**Results:** An 11 month-old boy presented with recurrent startling with axial contraction. He was born uneventfully from his healthy parents at a gestational age of 38 weeks weighing 2.87 kg. In past, he visited other hospital at 8 months of age due to global developmental delay without head control nor eye contact and hyperkinetic movements mimicking irritability or colic. Brain magnetic resonance imaging at that time was normal. On his first visit to our hospital, he could not do watch nor follow moving objects: he could do only fixate face on light intermittently. Electroencephalogram showed hypsarrhythmia. He was on vigabatrin and then was seizure free within a week. Metabolic screening including blood amino acid and urine organic acid analyses, chromosomal analysis and chromosomal microarray study produced no positive results. WES performed in the proband revealed the likely pathogenic, heterozygous inframe deletion of *GRIN1* (c.1561_1563del; p.Asn521del), which were verified with direct sequencing. This novel mutation was *de novo* as found in neither of his parents. His vision and development gradually improved on vigabatrin. Three months later, he can sit alone, can do eye contact and can watch and follow moving objects more than 180 degrees. Visual evoked potential test at 17 months of age was normal. However, his choreic and dyskinetic movements in his trunk and limbs were problematic in caring him.

**Conclusions:** The novel mutation of *GRIN1* were found in this proband with NDHMS, whose seizures were easily controlled, vision was markedly improved, and development had some improvement on vigabatrin.

# P3 - Expanding the phenotype of chromosome 4 duplication with dystonia and central non-ictal apnoea.

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**Introduction:**

Chromosome 1p36 deletion

• Features include developmental delay, seizures, visual problems, hearing loss, short stature, dysmorphism, brain anomalies, congenital heart defects and renal tract anomalies.

Chromosome 4p duplication

• Terminal copy number gains of the short arm of chromosome 4 are very rare with phenotype dependent on duplication size.
• Major features include facial dysmorphism, growth retardation and psychomotor developmental delay.

We present a 20-month old-boy, with the above aberrations,presenting with developmental delay, focal seizures, central (non-ictal) apnoeas and dystonia. The latter two features were not previously described as a part of either genetic abnormality.

**Case report:**

Early life:

• Emergency c-section at term for fetal distress.
• Diagnosed with ventriculoseptal defect, hypothyroidism, distinctive facial features, hypotonia and feeding difficulties.
• Failure to thrive (<0.4th centiles) and developmental delay since 2 months of age.
• CGH microarray: de novo copy number loss in ch1, region p36.33 to p36.31 and a de novo copy number gain within ch4, region p16.3 to 15.2 - arr[GRCh37] 1p36.33p36.31(834101_5887122)x1, 4p16.3p15.2(64577_21798253)x3 ~21.7Mb

Hospital stay:

• PICU admission at 5 months of age following respiratory arrest secondary to aspiration pneumonia.
• Following extubation developed focal right-sided seizures associated with apnoeas, thought possibly due to weaning from sedation.
• Standard EEG findings in keeping with hypoxic-ischaemic encephalopathy post respiratory arrest.
• MRI brain at 6 months old showed ischaemic lesions in left cerebellum and occipital region (basal ganglia were intact), which evolved into gliotic scarring with no parenchymal abnormalities, on repeat imaging at 8 months old.
• Continuing focal seizures at 7 months managed initially with levetiracetam and subsequently needing combination of sodium valproate and topiramate.
• Repeat EEG demonstrated focal epileptic discharges arising from left fronto-temporal region.

• PICU readmission a month later for focal status epilepticus.
• On discharge to HDU he had dystonic movements (not side-effects of medications) of the head along with jaw clenching and breath holding but remained responsive with reactive pupils. The episodes responded to a Gabapentin building regime.
• Subsequent investigations
a. Video telemetry: Focal electrographic seizures arising independently from both temporo-parietal regions. One of sub-clinical events was associated with SatO2=75% requiring bagging, suggestive of ictal hypoxaemia. Other desaturations (SatO2=80%) were not associated with EEG changes, suggestive of obstructive or central apnoeas.
b. Sleep study detected one central apnoea but no obstructive sleep events
• Genetic tests: epileptic encephalopathy gene panel – negative.
• Discharged home at 14 months of age on gabapentin, sodium valproate and topiramate.

Currently:

• Age 20 months, seizure-free on Topiramate (7.2mg/kg/day) and Valproate (40mg/kg/day).
• Improvement in dystonic movements on Gabapentin (54mg/kg/day).
• Remains on 0.2L nasal cannula oxygen with significantly less frequent desaturations.

**Conclusion:**

We propose that apart from all newly discovered monogenetic conditions causing the above-mentioned phenotypes, patients with complex neurological disorders (including developmental delay, seizures and movement disorders), should never be refrained from the classical first-tier diagnostic testing for chromosomal abnormalities, since structural chromosomal disorders are and will remain a substantial proportion of etiologic diagnoses in cases like ours.

# P4 - Successful treatment of recurrent hemiparesis caused by a heterozygote ATP1A3 variant with oxcarbazepine

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**Introduction**: Pathogenic variants of the ATP1A3 gene have been associated with a variety of neurological syndromes namely; alternating hemiplegia of childhood (AHC), rapid-onset dystonia parkinsonism (RDP) and Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy, and Sensorineural hearing loss (CAPOS) syndrome. As with several channelopathies genes, the phenotypic spectrum of ATP1A3 is expanding with non-classic presentations now described. AHC is a rare neurodevelopmental disorder characterized by repeated episodes of transient alternating hemiplegia and/or tetraplegia. Stringent diagnostic criteria have been described. A number of therapeutic agents are used with variable response including the calcium channel blocker flunarizine. Response to sodium channel blockers has not been previously documented.

**Methods**: We describe a 3-year-old boy whose clinical phenotype did not fully match that of AHC and had dramatically responded to oxcarbazepine.

**Results**: This left-handed Omani boy presented at the age of 3 years with an acute onset of right-sided body and facial weakness together with a slurred speech but with preserved consciousness. There was no history of a preceding seizure, trauma, vaccination or any infections. Investigations at the time were unrevealing including an EEG, brain MRI scan, head and neck MRA, cerebrospinal fluid (CSF) glucose and an echocardiogram. Gradual spontaneous recovery occurred within 3 days with no residual deficits. From there onwards, he continued to experience recurrent episodes of objective right-sided arm and leg weakness with ipsilateral facial weakness that lasted from a few hours to a couple of days. All episodesoccurred suddenly without any identifiable triggers or diurnal variations and were not associated with headache, loss of consciousness or unusual movements. Sleep did not particularly improve the episodes.

Past medical history was significant for neonatal-onset seizures. Those were neither investigated nor treated until they finally abated before the age of 2 years. His early motor development was mildly delayed and he had expressive speech delay when he first presented. Parents were non consanguineous and the family history was unremarkable.

A subsequent 3T brain MRI scan was normal apart from left mesial temporal lobe sclerosis. Repeated ictal and post ictal EEGs were normal. He was found to have a de novopathogenic p.Leu371Pro (L371P) (CTC>CCC): c.1112 T>C in exon 9 of the ATP1A3 gene.

He was commenced on oxcarbazepine the dose of which was maintained on 12mg/kg/dose. Since then all his episodes stopped completely and there had been a remarkable improvement in speech and cognitive development.

**Conclusion**: Mutations in the ATP1A3 should be considered in the differential diagnosis of recurrent transient hemiparesis even when the diagnostic criteria for AHC are not fully met. The ATP1A3 gene encodes the alpha-3 subunit of the Na+/K+ ATPase pump, which maintains electrochemical gradients of sodium and potassium ions across the plasma membrane. It is possible that oxcarbazepine plays a positive role in this mechanism.

# P5 - RHOBTB2 variant in a case of epileptic encephalopathy associated to paroxysmal movement disorder

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**Introduction**: Heterozygous variants in *RHOBTB2* gene cause early infantile epiletic encephalopathy type 64 (MIM #618004), which is characterized by seizures with onset in the first year of life, intellectual disability, poor motor development, and poor or absent speech. Additional features include hypotonia, movement disorder, and non-specific dysmorphic features. Disease severity is variable: some patients are non-verbal and non-ambulant, or unable to interact until early teenage years. *RHOBTB2* (MIM *607352) encodes for a member of the evolutionarily conserved RHOBTB-family of Rho GTPases.

**Methods**: Here we report a case of epileptic encephalopathy associated with paroxysmal movement disorder, due to a pathogenic variant in *RHOBTB2* gene.

**Results**: Case report: Our patient, now aged 8 years, was born at 34 weeks after normal pregnancy. Family history is reported negative for neurological disorders, but positive for psychiatric disorders in the father. Her clinical history is significant for onset of afebrile epileptic status at 3 months of age. She then presented other episodes of both febrile and afebrile epileptic status. She also presented global developmental delay. At two years of age she started presenting paroxysmal daily episodes of dystonic postures of the extremities followed by afinalistic dyskinetic movements without loss of consciousness. Brain MRI findings include brain atrophy, corpus callosum hypoplasia, and diffuse hypomyelination. She underwent an extended neurometabolic work-up: ammonia, serum and CSF lactate, urinary organic acids and mucopolysaccharides, plasma aminoacids, acylcarnitines, sialo-transferrins and very long chain fatty acids. Previous genetic tests include aCGH and direct sequencing for *SCN1A*, *MECP2*, *CDKL-5*, *FOXG-1*, *MEF2C*, *ATP1A3*, *PRRT2*, *SCLA2A1* and *PCDH-19* genes, all negative.

At 8 years, at clinical evaluation she appeared microcephalic, and hypotonic, with ataxic gait. Pharmacological treatment with carbamazepine resulted in the disappearance of the paroxysmal movement disorder.

Whole exome sequencing showed the heterozygous de novo missense variant c.1532G>A, p.(Arg511Gln) in *RHOBTB2* gene, previously reported as pathogenic.

The variant is predicted as damaging by in silico prediction softwares Polyphen, SIFT, and MutationTaster.

Variants in the *RHOBTB2* gene so-far listed as disease-causing in HGMD Professional 2019.3 are all missense and affect the amino acids 474-511, located in the BTB-domain-encoding region of RHOBTB2. No other likely pathogenic or pathogenic variants have been reported.

**Conclusions**: We present a patient with a neurological complex phenotype encompassing a epileptic encephalopathy, severe developmental delay and paroxysmal movement disorder (dystonic postures and hyperkinetic-dyskinetic movements). A pathogenic variant on the *RHOBTB2* gene was identified by whole exome sequencing.

# P6 - A distinctive SCN1A-related phenotype: multiple contractures, early onset epileptic encephalopathy and hyperkinetic movement disorder

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**Introduction**: *SCN1A* mutations occur in Dravet syndrome and genetic epilepsy with febrile seizures plus as the main epileptic phenotypes. Recently, a new phenotype has been described with early onset epileptic encephalopathy, profound developmental delay and hyperkinetic movement disorder. The most severe cases are evident in the first hours of life, with arthrogryposis and multiple paroxysmal events, including tonic spasms induced by tactile stimulation.

**Methods**: We report on a 2 year-old girl with this distinctive phenotype.

**Results**: The patient is the second child from a Romanian family. Both parents and her older sister are healthy. She was born at 27 weeks of gestation and experienced several complications due to prematurity, as respiratory distress syndrome, immaturity of gastrointestinal tract with failure to thrive, and late onset sepsis. At birth, she presented flexion contractures of elbows and knees as well as generalized stiffness. She also showed multiple paroxysmal motor events. The most frequent episodes were tonic spasms, which occur either spontaneously or after tactile stimulation. They did not respond to benzodiazepines. In addition, there were diaphragmatic myoclonic jerks, which could last for more than 15 minutes. Repetitive EEG recordings did not show ictal nor interictal abnormalities. Brain MRI only disclosed small focal areas of hyperintensity surrounding the lateral ventricles, suggestive of periventricular calcifications. Genetic analysis ruled out hyperekplexia. The spasms were fairly controlled with oxcarbazepine. An extensive metabolic work-up was negative. Finally, genetic testing by Whole-Exome Sequencing detected a heterozygous de novo mutation in *SCN1A* gene: c.4036T>C (p.S1346P). This variant is not previously reported, but it is classified as likely pathogenic. Oxcarbazepine was suspended, but at 4 months of life she presented clonic jerks and, for the first time, epileptic discharges were registered on EEG recording. Besides, there were long lasting episodes of stiffness and impaired awareness seizures. Levetiracetam and zonisamide achieved a partial response. Developmental milestones were delayed, but at 17 months she experienced a neurological regression losing previously acquired skills. She was unable to control her head or grasp objects. EEG recording showed hypsarrhythmia and she received ACTH followed by vigabatrin. One month later a hyperkinetic movement disorder appeared. She had choreoathetosis as well as facial dyskinesias. Nowadays she is 2 years-old. Flexion contractures have improved. However, developmental delay is profound. Non-verbal communicative intention is reduced. She is unable to hold her head up due to axial hypotonia, but she has started to use her hands. Hyperkinetic movements are continuous and epileptic seizures persist. Brain MRI displays global atrophy.

**Conclusions**: *SCN1A* is the most relevant epileptic gene. The case we have presented expands the clinical spectrum. In newborns with arthrogryposis and early onset paroxysmal events (epileptic and non-epileptic) *SCN1A* encephalopathy should be suspected. The prognosis is more severe than in Dravet syndrome.

# P7 - Movement Disorders and Epilepsy in Four Forms of Neuronal Ceroid Lipofuscinosis (NCL)

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**Introduction:** The Neuronal Ceroid Lipofucinoses (NCLs) are rare, inherited, fatal lysosomal diseases of childhood caused by mutations in various genes. Although NCLs comprise more than 12 distinct diseases, key common features include vision loss, epilepsy, progressive dementia and movement disorders. The specific movement disorders and specific manifestations of epilepsy may vary across forms, but it is not known whether or how the movement disorder and epilepsy manifestations may be linked within or across NCLs. Our objective was to quantify the prevalence of each type of movement disorder and seizure in CLN1, CLN2, CLN3, and CLN6 diseases and determine whether the severity of movement disorders and seizures are correlated.

**Methods**: To quantify types and severity of movement disorders and seizures in the CLN1, CLN2, CLN3, and CLN6 forms of the NCLs, we used data from longitudinal studies employing the Unified Batten Disease Rating Scale (UBDRS). The types of movement disorders present were determined by neurological examination and standard definition of movement disorder phenomenology. Presence and severity were rated for each of the following: dysmetria, parkinsonism (increased tone, bradykinesia, tremor, postural instability, and gait disorder), chorea, myoclonus, tics, and dystonia. The types, frequency, and (when relevant) duration of post-ictal period were determined from parent report and clinical description for each of the follow: generalized tonic-clonic (GTC), myoclonic, atonic, complex-partial / absence, and simple partial. Types of movement disorders and seizures in each NCL were compared using chi-square analyses. Relationships among movement disorder and seizure severities for each NCL form were evaluated using linear models.

**Results**: We have collected cross-sectional or longitudinal UBDRS data from participants with genetically-confirmed CLN1 (n=12), CLN2 (n=21), CLN3 (n=134), and CLN6 (n=7) diseases. Both a movement disorder and epilepsy were present at the time of evaluation in the majority of individuals with CLN1 (9/12), CLN2 (20/21), CLN3 (91/134), and CLN7 (5/7). The most prevalent type of seizure was myoclonic in CLN1 and GTC in CLN2, CLN3, and CLN6. The most prominent movement disorder type was parkinsonism in CLN1, CLN3, and CLN6. Myoclonus and parkinsonism were equally present in CLN2 disease. Overall movement disorder severity did not correlate with overall epilepsy severity in any form of NCL, but the severity of GTC seizures specifically correlated with parkinsonism in CLN3 disease ($r=0.4$; $p<0.001$).

**Conclusions**: The CLN1, CLN2, CLN3, and CLN6 forms of the NCLs are characterized by presence of both a movement disorder and epilepsy in most affected individuals. However, each form of NCL has a characteristic pattern of movement disorders and seizures types. Despite the presence of both types of symptoms, there is no relationship between movement disorder severity and epilepsy severity. These data suggest that while seizures and MDs are highly prevalent in NCLs and both worsen with progression, they represent separate pathophysiological processes that have independent determinants of severity.

# P8 - The case of severe infantile epileptic encephalopathy caused by bi-allelic mutation in the UGDH-gene.

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**Introduction:** West syndrome is a severe epilepsy syndrome composed of: infantile spasms, an interictal electroencephalogram pattern termed hypsarrhythmia, and mental retardation. The long-term overall prognosis for patients with infantile spasm is poor. It is still heavily related to the condition's etiology.

**Methods**: We report the case of a child, who admitted to neurological department at the age of 5 months 3 weeks with the infantile spasms, absent signs of motor and cognitive development. The investigation focused on analysis of clinical, neurovisualisation, EEG and laboratory findings.

**Results**: Perinatal anamnesis showed no complication. However, the child had weak sucking from birth. It was bottle-fed from the age of 1,5 months. Such early developmental milestones as following with eyes, smiling, babbling, turning to a side or tummy were not achieved. The infantile spasms appeared at the age of 3 months but they were not timely recognized as an epileptic events. The global developmental delay and infantile spasms up to 10-12 series per day were noticed at the admission in the age of 5 months 3 weeks. At that point hypsarrhythmia was reported on interictal EEG and 1,5T MRI didn't reveal abnormality. The diagnosis of West syndrome was made on admission with following trial of vigabatrin, pyridoxine, ACTH, valproic acid which failed in terms of controlling seizure events. On the follow up the sucking deteriorated, axial hypotonia with limb spasticity developed, hyperkinetic movements in the arms and myoclonic jerks in the legs appeared. The administration of ACTH was complicated by development of pneumonia and pyoderma. Within 6 weeks from the beginning of treatment the infantile spasms were changed by focal to bilateral tonic-clonic seizures with frequency up to 10 per day. The discontinuation of hormonal treatment and prescription of phenobarbitone resulted in stabilization of the patient and reduction of seizures for a short period of time. The second interictal EEG at the age of 7 months registered discharges of spike-waves in the left occipital and temporal areas, singular generalized spike-waves. Second 1,5 T MRI around the same time revealed pathological changes of signal: hypertense T2W and diffusion restriction DWI in globus pallidus, thalamus, dorsal parts of midbrain, pons along lemniscus medialis; global brain atrophic changes were evident. Invitae epilepsy gene panel identified variants of unknown significance in ALDH5A1 and PRDM8 genes. Further genetic investigations revealed that the patient carries bi-allelic mutation in the UGDH gene: p.Arg442Trp is inherited from the mother and p.Arg443His is inherited from the farther. At the age of one year the patient demonstrated no progress in development apart from short-time eye focusing and recovering of enteral feeding without naso-gastral tube. The one has multiple daily focal to bilateral tonic-clonic seizures despite recent initiation of ketogenic diet treatment.

**Conclusion**: The current patient with probable UGDH related epileptic encephalopathy demonstrated pharmacological resistance to all conventionally used drugs for the treatment of infantile encephalopathy.

# P9 - KCNH1 related syndrome presenting with oculomotor apraxia and ataxia: a case report

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**Introduction:** KCNH1 encodes a voltage-gated potassium channel (Eag1-kw10.1) with prominent expression in the brain. Its mutations have been found to be pathogenic in two rare syndromes: Zimmermann Laband and Temple-Baraister, both characterized by dysmorphic facial features, thumb and skeletal anomalies, epilepsy and intellectual disability. Moreover KCNH1 gene has been involved in few uncharacterized intellectual disability cases.

**Case Report:** we report on a girl with a missense de novo KCNH1 mutation (Gly496Arg), presenting with movement disorder (ataxia and oculomotor apraxia) as first and prominent symptom since age 18 months.

One year later she developed epilepsy not responsive to phenobarbital and levetiracetam but then completely controlled by carbamazepine treatment.

Nowadays, at age 8 years she is seizures free with CBZ monotherapy; she has intellectual disability (WISC-IV IQ 44), mild ataxia and oculomotor apraxia.

Her EEG shows generalized background slowing and multifocal epileptiform abnormalities. She doesn't have any dysmorphic facial features, nor nail hypoplasia or skeletal anomalies.

**Discussion:** from OMIM review we found 12 patients with KCNH1 related syndromes, most of them diagnosed with Zimmermann Laband syndrome. Clinical phenotype appears quite heterogeneous: epilepsy is a key manifestation with both generalized and focal motor seizures, varying from responsive to monotherapy to drug-resistant seizures, intellectual disability is always present while dysmorphic features (facial or skeletal) are very variable.

We highlight the peculiarity of our case: showing as first prominent symptom a movement disorder (ataxia and oculomotor apraxia), with epilepsy onset one year later and no dysmorphic features at all, thus expanding further the phenotype of KCNH1 related syndromes.

# P10 - Recognizing the phenotype of "GNAO1-associated encephalopathy": when to suspect this genetic condition

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**Introduction:** Mutations in GNAO1 (guanine nucleotide binding protein, alpha activating activity polypeptide O) were first reported in patients with Ohtahara syndrome and early infantile epileptic encephalopathy. More recently, a syndrome of neurodevelopmental disorder with involuntary movements with or without epilepsy has been defined, expanding the phenotypic spectrum of GNAO1 mutation-associated neurological disorders. GNAO1 encodes Gαo, a member of the G protein signal transducers considered the most abundant and important membrane protein in the central nervous system, as it plays major roles in synaptic neurotransmission and neurodevelopment.

**Methods**: Retrospective descriptive study. Case series of a single center experience in GNAO mutation-associated syndromes since 2017.

**Results**: All the patients presented with hypotonia and abnormal movements in early infancy after an unremarkable perinatal course.

*Patient 1* (14 y.o., male). He inicially presented at age three months with multifocal dystonia, orofacial dyskinesias and later on choreoathetosis. He had poor head control and a weak suck and required gastrostomy tube feedings. He had no expressive or receptive language. He never had seizures. He was diagnosed with status dystonicus requiring intensive care unit admission triggered by pneumonia. Brain MRI and EEG were normal. He had poor response to benzodiazepines, neuroleptics, topiramate and carbamazepine. At the age of 14, deep brain stimulation was perfomed and he experimented a significant improvement in terms of choreothetosis and dyskinesias.

*Patient 2* (10 y.o, male). His first symptom was purpose dystonia at the age of 12 months. He was able to achieve head control but never had a stable sitting posture or expressive speech. He had no dysphagia or seizures. Brain MRI and EEG were normal.

*Patient 3* (7 y.o, female). She presented with dystonia and choreoathetosis at age 15 months. She developed severe exacerbations of chorea with a prominent autonomic component triggered by infections. She achieved head control but was unable to get a stable sitting posture or develop any speech milestone. She had seizures in early infancy that were well controlled on levetiracetam. Brain MRI revealed a lacunar stroke and global atrophy and EEG was normal. She partially improved with benzodiazepines, neuroleptics and topiramate. At the age of 6, deep brain stimulation was perfomed and she experimented an improvement in terms of chorea.

*Patient 4* (6 y.o, female). She presented in early infancy with motor delay, dystonia and choreoathetosis at age 5 months, after a febrile respiratory infection. She had severe dysphagia and required gastrostomy tube feeding. She did not develop language and never had seizures. Brain MRI and EEG were unremarkable.

**Conclusions:**

- The phenotype of mutations in GNAO1 is complex but seems to involve global retardation of cognitive and predominant motor development, with or without epilepsy.

- In patients with early onset of movement disorders, particularly dystonia and choreoathetosis, GNAO-associated syndromes should be ruled out.

- Exacerbations of chorea and dystonia lasting hours to days with prominent dysautonomia triggered by infection, anxiety or emotional stress can occur in GNAO1-associated encephalopathy.

- In patients with a suboptimal response to medications, deep brain stimulation can improve the symptoms.

# P11 - Early infantile SCN1A epileptic encephalopathy: a combination of epileptic encephalopathy and hyperkinetic movement disorder

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**Introduction:** In the last years, there has been increasing recognition of the overlap between developmental/epileptic encephalopathies and movement disorders.

*SCN1A*-related disorders include Dravet syndrome (DS), genetic epilepsy with febrile seizures plus (GEFS+), and familial hemiplegic migraine as the main phenotypes. However, a novel phenotype with early onset epileptic encephalopathy, profound developmental delay and an hyperkinetic movement disorder was recently described, mainly in association with the missense mutation p.Thr226Met.2

**Methods**: We describe the clinical, EEG, neuroimaging and genetic data in a patient with a likely pathogenic variant in the *SCN1A* gene and a complex neurologic phenotype.

**Results**: We report on a 6-years-old boy, born from healthy unrelated parents at 35 weeks of gestational age following uneventful pregnancy and delivery. At 20 h of life he was admitted to the neonatal intensive care unit because of stiffness, multiple contractures, hip dysplasia and talipes. He also presented with frequent episodes of tonic spasms occurring mainly in response to tactile stimuli since the first hours of life. As serial EEGs were unremarkable, hyperekplexia was suspected and clonazepam introduced with unsatisfactory results. Carbamazepine progressively controlled these episodes. Neonatal brain MRI and EMG were negative. At 8 months of age he presented with a prolonged hemiclonic seizure, followed by Todd's paralysis. He developed severe psychomotor delay with absent speech, and a severe, pharmacoresistant epileptic encephalopathy with multiple seizure types (atypical absences, focal motor and bilateral tonic-clonic seizures, episodes of myoclonic status epilepticus), with fever susceptibility. He is severely hypotonic (unable to sit) with proximal limb retractions and displays very poor voluntary motor repertoire. From 20 months of age, he has developed a prominent hyperkinetic movement disorder (choreoathetosis and distal myoclonic jerks, with paroxysmal exacerbations accompanied by dystonia). Follow-up EEGs demonstrate focal epileptiform discharges over the anterior regions and progressive deterioration of background activities, paralleling the development of cortical atrophy on brain MRIs. Negative genetic investigations include direct sequencing of: *GLRA1*, *CRFL1*, *SCN4A*, *PRRT2*, *SCN2A*, *CLCN1*, *ARHGEF9*, *SLC2A1*, *ATP1A3*, *CACNA1A*, *POLG1*, *UBE3A*, and *KCNQ2*. Array-CGH is non-contributory. He underwent an extended neurometabolic work-up: ammonia, serum and CSF lactate, urinary organic acids and mucopolysaccharides, plasma aminoacids, acylcarnitines, sialo-transferrins and very long chain fatty acids, CSF neurotransmitters, serum auto-antibodies (anti-NMDAR, LG1, CASPR and GABA2), skin and muscle biopsy (histology and mitochondrial respiratory chain activity): all normal.

Molecular testing for the *SCN1A* gene documented the heterozygous, de novo missense c.628T>C (p.Ser228Pro) variant, classified as likely pathogenic. The variant is absent from Genome Aggregation Database, predicted to be deleterious by the in silico prediction tools SIFT and MutationTaster (tolerated by PolyPhen) and reported in ClinVar as likely pathogenic (ID375512).

**Conclusions**: We describe a case sharing various clinical features with previously described patients with early infantile *SCN1A* epileptic encephalopathy: early-onset, severe developmental encephalopathy resulting in profound developmental delay, pharmacoresistant epilepsy with multiple seizure types, prominent hyperkinetic movement disorder, non-specific neuroimaging findings.

# P12 - Long term survival in a patient with GF1M gene mutation

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**Introduction:** Defects caused by mutations in the nuclear genes involved in the mitochondrial translation system, can cause a heterogeneous clinical phenotype, with early onset of neurological disorders and often with a fatal outcome due to organ failure.1 *GFM1* (MIM# 606639) encodes one of four translation elongation factors in mitochondria, EFG1 or mtEFG, which catalyzes the translocation of peptidyl-tRNAs from the ribosomal A site to the P-site during the elongation phase of mitochondrial translation.

**Methods:** We here present a patient with a previously reported pathogenic variant on *GFM1* gene and a long term survival.

**Results**: Case report: Our patient, now aged 12, was born at 38 weeks of gestational age after normal pregnancy. Neonatal weight was 2750 gr, cranial circumference was 33 cm (< 3 °p). On day two of life, he was hospitalized for respiratory distress with need of oxygen therapy. His clinical history is significant for microcephaly and dysmorphic traits with syndactyly, and developmental delay. At 6 months of age, he started presenting, mainly during wakefulness, epileptic seizures (epileptic spasms). At clinical evaluation was also noted axial hypotonia and a spastic/dystonic tetraparesis.

Antiepileptic treatment with phenobarbital was then started. Due to the persistence of epileptic seizures (i.e. asymmetric tonic versive seizures and tonic spasms), antiepileptic polytherapy was necessary. Electroencephalography showed poorly formed background activity with multifocal epileptic abnormalities. Biochemical tests showed persistent lactic acidosis, urine organic acids showed excessive excretion of 2-ketoglutaric acid and 4-OH phenylacetic acid. Brain MRI revealed cerebellar hemispheric hypoplasia, mega cisterna magna, supratentorial white matter reduction, polymicrogyria, and progressive emispheric atrophia. Mithocondrial respiratory chain enzymatic activity and pyruvate dehydrogenase activity tested on muscle biopsy, showed normal results. Human skin fibroblast culture showed decreased enzyme activity for IV OXPHOS complex.

Direct sequencing for *POLG1* and *CDKL5* genes, next generation sequencing (NGS) epilepsy panel, as well as white matter disease panel and array CGH have been tested with normal findings. Whole genome sequencing led to the identification of a variant on *GFM1* gene c.748C>T, p.(Arg250Trp). Simon and his colleagues (2017) described two brothers harbouring the same Arg250Trp variant in a compound heterozygositis, one presenting a severe disease course and the other brother with a milder phenotype. The same *GFM1* variant has previously been reported by Smits et al. (2011) in a patient with severe, rapidly progressive mitochondrial encephalopathy with death at 2 years of age.

**Conclusions:** So far only 27 patients have been reported with pathogenic variants in *GFM1* gene. Many of the previously reported patients died during the two first years of life. A recent report include 9 patients with *GFM1* gene mutations and a predominant neurologic involvement and 6 of the reported cases present a long term survival. We present a 12 years of age patient with a severe neurological disease, associated with a stable metabolic course leading to a long term survival. The neurologic phenotype of our patient is consistent with an early infantile epileptic encephalopathy and movement disorder mainly characterized by dystonic postures.

# P13 - Pantothenate Kinase-Associated Neurodegeneration (PKAN) In Saudi: A Phenotypic Characterization and Novel Mutations

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**Introduction**: The term neurodegeneration with brain iron accumulation (NBIA) is used to describe a group of inherited neurodegenerative movement disorders characterized by an accumulation of iron in the basal ganglia. As a result, these patients typically present with progressive dystonia, spasticity, parkinsonism, psychiatric and eye abnormalities. Their brain MRI classically exhibits the pathognomonic “eye-of-the-tiger” sign. Several types of NBIA have been identified with pantothenate kinase-associated neurodegeneration (PKAN) being the most frequent type. PKAN is a rare autosomal-recessive disorder caused by mutations in the pantothenate kinase 2 gene (PANK2), located on chromosome 20p. PKAN can present clinically in two major forms, typical PKAN, exhibiting early pediatric onset and atypical PKAN, characterized by late onset and a slower disease progression.

**Methods**: This was a retrospective cohort of 21 Saudi patients diagnosed with PKAN and managed at KFSH&RC between 1990-2019.

**Results**: Sixteen patients had typical PKAN and five exhibited atypical PKAN. Among the typical presentation group, the average onset age was 2.21 years. The majority of them presented initially with walking problems in the form of tiptoeing in 9.5% (n=2), gait unsteadiness in 19% (n=4) and frequent falls in 33.3% (n=7). Furthermore, dystonia was prevalent among them and presented initially in the form of oromandibular dystonia in 14.3% (n=3), axial dystonia in 4.8% (n=1), upper limb dystonia in 14.3% (n=3), and cervical dystonia in 14.3% (n=3). Lower limb dystonia was not observed at onset in this group. Motor regression affected 9.5% (n=2) of them and speech regression was observed in 9.5% (n=2). Genetically, a diverse number of homozygous mutations were detected among this group, out of which c.1231G>A:p.Gly411Arg was the most common mutation accounting for 14.3% (n=3) of the cases. Notably, one of the patients in this group was found to exhibit a novel mutation (c.916 G>A P.Gly306Arg). Furthermore, 19% (n=4) underwent deep brain stimulation (DBS) resulting in partial or significant improvement in their condition.

In contrast, the five atypical patients diagnosed with late-onset of PKAN had the same novel homozygous mutation (c.767 C>T,p.256pro>Leu) which is not reported before. Their average age of onset was 14.2 years. They all presented initially with dystonia in one of the limbs, 60 % of which were in the lower limb (n=3). Oromandibular dystonia was present initially in 20% (n=1). Language regression was observed initially in 20% (n=1). This mutation seems to be associated with a milder phenotype and a slower progression with all patients surviving till teenage age. Ambulation loss and dysarthria were not observed until late in the disease course. The oldest of the patients (n=1) passed away at the age of 28 years. A second patient passed away at the age of 19 years. The remaining patients (n=3) are still alive with the youngest being 13 years old.

**Conclusion**: We reported the phenotypical characteristics of a diverse group of typical and atypical Saudi PKAN cases among which two of mutations, up to our knowledge, are reported for the first time.

# P14 - Movement disorders in early onset epileptic encephalopathies: a comprehensive literature review

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**Introduction**: Early onset epileptic encephalopathies (EOEE) are severe brain disorders of early age. They manifest with seizures, usually intractable and associate cognitive, behavioral and neurological deficits that can be relentless, and sometimes provoke premature death. Associated movement disorders are, in many of these cases, a key part of the disease.

**Objectives**: The objective of this study is to describe the characteristics of movement disorders reported in children with EOEE and to elaborate an algorithm that could facilitate the clinical diagnosis of these disorders.

**Methods**: The patients included were up to 18 years old and were affected by one (autosomal dominant) or two variants (autosomal recessive) in one of the 77 genes included in the list of the phenotypic EOEE series of Mendelian Inheritance in Men (OMIM). Clinical, genetic and radiological characteristics were collected from prospective cohort studies or clinical cases of the PubMed database dated until September 2019 following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

**Results**: 1713 out of 14462 studies met inclusion criteria. 1206 patients (media±SD:0,84 ±2,06 years, age range: neonatal period -18 years old) were included. Most of the patients exhibited moderate to profound intellectual disability. Twenty five percent of the patients presented movement disorders. Dystonia, choreoathetosis, stereotypies and ataxia were the most frequent movement disorders. Status dystonicus was reported in patients with variants in ARX, GNAO1 and SCN8A. In 73% of patients, brain MRI was abnormal, including cerebral or cerebellar atrophy, delayed myelination, dysgenesis of the corpus callosum and malformation of cortical development.

**Conclusion**: The description of movement disorders in the articles included is suboptimal, therefore a systematized reporting procedure should be established. There are some recognizable clinical radiological phenotypes that can guide the genetic diagnosis.

# P15 - Biallelic variants in CSTB cause a developmental and epileptic encephalopathy with dyskinesia

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**Introduction:** Biallelic *CSTB* (cystatin B) variants primarily cause Unverricht-Lundborg disease, a type of progressive myoclonic epilepsy. The vast majority of cases (90-99%) have two dodecamer repeat expansions in the promoter region, with the remainder caused by a single dodacamer repeat plus a single nucleotide variant (SNV) or indel. More recently, four patients in two families with homozygous *CSTB* variants causing premature stop codons were described with severe developmental delay, microcephaly, movement disorders, seizures, hypomyelination and cerebral atrophy.

**Methods:** Patients with biallelic SNVs or indels in *CSTB* were identified either at Texas Children's Hospital or by searching for additional cases in the Center for Mendelian Genomics, Baylor Genetics Laboratory and GeneDx databases. All probands were diagnosed via index or trio exome sequencing or targeted panel testing approaches with confirmation by Sanger sequencing.

**Results:** We identified an additional seven patients with severe infantile-onset neurodevelopmental disease and biallelic *CSTB* SNVs and/or indels. All presented in the first year of life with developmental concerns. All had microcephaly and severe developmental delay. Only one patient achieved independent sitting and feeding. Importantly, five out of seven patients exhibited developmental regression between five months and three years of age, often losing all previously acquired skills. Regression followed a hospitalization for pneumonia in one case and co-occurred with seizure onset in another two. All patients had a hyperkinetic movement disorder, including dystonia, chorea and myoclonus. Five out of seven had seizures, typically tonic or myoclonic, and two had medically refractory epilepsy. All exhibited hypotonia, and most developed appendicular hypertonia (spasticity or dystonia) with time. Brain MRI features included immature sulcation, hypomyelination, and reduced brain volume. In cases where serial imaging was available, progressive cerebral atrophy was apparent. Molecular analysis revealed c.[202C>T];[67-1G>C] (1 patient), c.[67-1G>C];[c.10G>A] (1 patient), c.[202C>T];[66+2T>C] (3 siblings), homozygous c.67-1G>C (1 patient), and c.[1_2insAT];[c.67-1G>C] (1 patient). [c.10G>A] and [66+2T>C] represent novel variants.

**Conclusions:** Biallelic deleterious variants (frameshift, splice-site or missense variants affecting critical domains) in *CSTB* cause a progressive, severe developmental and epileptic encephalopathy with dyskinesia distinct from Unverricht-Lundborg disease. This condition is characterized by severe developmental delay, microcephaly, a hyperkinetic movement disorder, epilepsy, hypotonia, hypomyelination and progressive cerebral atrophy.

# P16 - GNAO1-assocoated movement disorders in Hong Kong: a case series of 5 families

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**Introduction**: The molecular mechanism of *GNAO1*-related movement disorder is further demystified to-date. Both gain-of-function (GOF) and loss-of-function (LOF) variants had been described with different clinical features which GOF variants are associated with movement disorder while LOF variants are associated with epileptic encephalopathy. Here, we reported 5 unrelated cases in Hong Kong with 3 cases affected by the GOF mutations and 2 cases affected by the LOF variants.

**Methods**: Cases were referred to us through the first Undiagnosed Diseases Program (UDP) in Hong Kong which was supported by the S. K. Yee Medical Foundation. Clinical genetics and genomics analyses included conventional PCR and Sanger sequencing and clinical whole exome and genome sequencing (CWES and CWGS). Bioinformatics analysis was done using in-house algorithm. The interpretation was based on clinical, laboratory and imaging findings, and pathomechanism of *GNAO1* gene.

**Results**: The age of onset ranged from 8 days old to 3 years old. Case 1 is a 12 years old girl who presented with involuntary movement at 8 years old. Case 2 is a 13 years old boy who presented with cerebral palsy at < 1 year old and was suspected to have cerebral folate deficiency. A heterozygous *GNAO1* pathogenic variant, c.736G>A; p.Glu247Lys was detected in both cases 1 and 2. Case 3 is a 10 years old boy who first presented with severe involuntary movement at 3 years old with suspected dopa-responsive dystonia. A novel heterozygous pathogenic variant, c.137A>G; p.Lys46Arg was identified. Case 4 is a 6 years old girl who first presented with intractable epilepsy at 8 days old. A heterozygous variant, c.118G>A; p.Gly40Arg was identified. Case 5 is a 19 years old woman who first presented with intractable epilepsy and global developmental delay at 2 months old. Mitochondrial disorder was suspected. A novel heterozygous pathogenic variant, c.134G>A; p.gly45Glu was identified.

The c.735G>A; p.Glu247Lys is a known GOF pathogenic variant while the c.118G>A; p.Gly40Arg is a reported LOF pathogenic variant. The variants c.137A>G; p.Lys46Arg and c.134G>A; p.gly45Glu are novel pathogenic variants and we predicted the c.137A>G is a GOF variant and c.134G>A is a LOF variant based on the clinical presentation of cases 3 and 5 respectively.

**Conclusions**: Clinical WES can streamline genetic analysis and sort out pathogenic genes in an unbiased approach. *GNAO1* is a disease-causing gene for the autosomal dominant neurological disorder for both GOF and LOF variants. The novel pathogenic variants identified in this case series should contribute to our understanding of the expanding spectrum of GNAO1-related disorders.

# P17 - PEDiDBS 2020: Update on the international registry of pediatric patients undergoing deep brain stimulation

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**Introduction**: Deep brain stimulation was first approved for pediatric use in the United States in 2003. Sixteen years later, it continues to have Humanitarian Device Exemption status for dystonia, indicating that only a small number of patients (< 4000) under the age of 18 have been implanted. This is reflective of worldwide experience. There are few dedicated pediatric centers performing DBS. Most children continue to be implanted at centers primarily focused on adult care. Surgical techniques have evolved however many questions remain regarding the role of DBS in pediatric patients. These questions can best be addressed by collaborative data sharing.

**Methods**: An international collaborative of investigators met several times between 2013 and 2016 to develop a mechanism for data sharing in order to help guide understanding of the role of DBS in children and adolescents. The result of those meeting is PEDiDBS, the international registry of children undergoing DBS. Finding an acceptable platform for secure data sharing and subsequent changes in international privacy laws proved more difficult than anticipated. These hurdles have been overcome, and PEDiDBS is now ready to begin site activation and patient data entry.

**Results**: Subjects are entered utilizing a de-identified limited data set and data is stored on a secure REDCap cloud server. Data entry is straightforward. There are fields for demographics including genetic information when available and surgical implant information. Follow-up information including therapeutic response and complications are entered over time. Once a page is reviewed for completeness and consistency, that part of the data will be locked to further changes in order to preserve the integrity of source information used in analysis.

Each site, identified by number, enters its own data and is therefore responsible for ensuring accuracy and maintains access to its own data. Aggregate data for analysis by participating sites can be requested through the data sharing committee. Nearly two dozen centers have expressed interest in participation. An initial study comparing DBS outcomes in genetic vs. environmentally-mediated dystonia is beginning.

**Conclusion**: There is an expanding role for DBS that now includes movement disorders, epilepsy and neuropsychiatric syndromes. PEDiDBS represents an important method of further elucidating the role of deep brain stimulation in pediatrics. Full information on participation is available on the website, www.PEDiDBS.org.

# P18 - Expanding the phenotypic spectrum of FOXG1 syndrome

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**Introduction**: FOXG1 syndrome is a rare neurodevelopmental encephalopathy. There are two clinical phenotypes/syndromes identified in FOXG1 syndrome, duplications and deletions/intragenic mutations. In children with deletions or intragenic mutations of FOXG1, the core symptoms are characterized by microcephaly, brain structural anomalies, early onset hyperkinetic movement disorders, epilepsy, and severe cognitive impairment. There were less than 150 reported cases worldwide. In this study, we described the clinical characteristics of FOXG1 syndrome, with the intragenic mutations in 5 patients.

**Methods**: We retrospectively reviewed the clinical characteristics as well as genetic mutations in five FOXG1 syndrome in a cohort of Rett/Rett mimicking syndrome in our pediatric movement disorder clinic.

**Results**: In our cohort, which consists of approximately 60 patients, five patients harboring FOXG1 mutations were identified (c.763 T>C, c. 250delC, c.256dupC, c.763_893del and c.645 C>A). All of the mutations were classified as pathogenic or likely pathogenic variants according to ACMG guidelines. There are 4 males and 1 female, with age 2.7 years old-18years old. All of them have early onset developmental delay with onset between 2-4 months of age. For the 4 males, all of them have epilepsy, including generalize and focal seizure, with onset age between 1-2.6 years. All of them have different degree of dysgenesis of corpus callosum and underdevelopment of frontal areas. In addition, they also have early onset hyperkinetic movement disorders and hand stereotypies. Of note, in the oldest patient (now 18 years old), there is an evolution of movement disorders with age (from hyperkinetic movement to rigidity and dystonia in his adolescence). For the female patient, there is a clearly distinctive clinical presentation. Currently at the age of 4.3 years, she has normal head circumference and brain MRI. Although she also has early onset developmental delay, but there are no obvious hyperkinetic movement disorders, such as chorea athetosis nor hand stereotypies. Ataxic gait is the only movement disorder. There is no epilepsy.

**Conclusions**: Individuals with FOXG1 syndrome may show clinical progression from hyperkinetic to hypokinetic features over time. In addition, some may only present with ataxia. Our patients expand the phenotypic spectrum of FOXG1 syndrome. FOXG1 mutation may be consider to add into the differential diagnosis of the childhood-onset ataxia.

# P19 - Eye movement disorders in children with epilepsy: study from one University Hospital in Taiwan

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**Introduction**: Children with epilepsy are frequently associated with movement disorders. However, they are rarely associated with eye movement disorders, and were rarely reported in the past.

**Methods**: We investigated the eye movement disorders in children with epilepsy and genetic mutation in our hospital.

**Results**: Total five patients with genetic epilepsy and eye movement disorders were found. Two with SATB2 mutations presented with infantile spasms. The eyes showed intermittent esotropia, which got worse after treatment with ACTH. They improved months after ACTH treatment, and persisted for years. Another one with QARS1 mutation and infantile spasms showed pathological paroxysmal tonic downgaze, which also got worse after the use of ACTH. One with IRF2BPL mutation and epilepsy also showed intermittent esotropia. Another one with BRAF mutation revealed prolonged eyelid blinking for 20 minutes after tactile stimulation (prolonged hyperekplexia).

**Conclusions**: Eye movement disorders are not difficult to find and may remain unnoticed by most neurologists. Pay attention to the presentations may broaden the clinical phenotypes of children with epilepsy due to genetic mutations.

# P20 - Action myoclonus and mental deficiency in a patient with a SCN8A splicing mutation

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**Introduction**: *SCN8A* mutations may cause developmental and epileptic encephalopathy. The clinical picture may include myoclonus, which can be part of the epileptic manifestation (myoclonic absences or myoclonic seizures); however also cortical myoclonus has been reported (Gardella et al, 2018). In only one family with partial loss of function of the SCN8A gene, myoclonus was not associated with epilepsy and it was judged to have a subcortical generator (Wagnon et al, 2018).

**Case report**: We describe a 25 years old woman, with action myoclonus and moderate mental deficiency, coming from Congo.

She is the third of four siblings, from non-consanguineous parents. No familiarity for neurological diseases is reported.
She was born after uneventful pregnancy and delivery.
She manifested a delay in speech acquisitions and early-onset stuttering, and difficulties in learning, reading and writing.

At 14 years, mild tremor-like hyperkinetic movements of the hands were noted.
At 16 years, a formal IQ assessment (scale Leiter-R) showed a value 45.
At 18 years, a neurological exam showed distal myoclonic tremor during postural maintenance and voluntary movements; global clumsiness without clear signs of ataxia.

No therapy was started for movement disorder. In the following years, myoclonic tremor gradually worsened causing impairment in several daily activities (difficulties in using cutlery at the table and incomprehensible writing).

Repeated EEG recordings showed diffuse slow waves, and few sharp waves on fronto-central areas. Simultaneous EMG recordings from distal upper limb muscles showed repetitive bursts, which were synchronous on antagonist muscle couples and recurred at a frequency around 15 Hz. Somatosensory evoked potentials showed increased amplitude of the cortical components. EEG-EMG analysis showed a significant coherence between central EEG derivations and the contralateral EMG around 15 Hz, suggesting a cortical origin of the jerks.

Next Generation Sequencing (NGS) analysis of a panel containing 188 genes related with epileptic encephalopathies and myoclonus epilepsies showed the presence of the nucleotide variation c.2544+1G>A in the SCN8A gene, resulting in splicing defect.

**Conclusions:** In our patient, cortical myoclonus was a characteristic sign associated with mental retardation but not epilepsy.

# P21- Genetic Syndromes with Movement Disorders and Epilepsy: a single-centre experience

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**Introduction**: The association of epilepsy and movement disorder has been described in many syndromes, due to chromosomal rearrangements or gene mutations. Some of these conditions are well defined and the characteristics of epilepsy and movement disorders are well known. The aim of this study was to investigate the prevalence of the co-occurrence of epilepsy and movement disorders in children harboring genetic mutations or copy number variations (CNV) and to describe their clinical phenotypes.

**Methods**: We retrospectively analyzed our data bases of pediatric patients who underwent genetic tests. These data bases include patients tested by single gene Sanger sequencing (from 2009 to 2019), by Next Generation Sequencing (NGS) gene panels (from 2014 to 2019) or by array-based comparative genomic hybridization (array-CGH, from 2009 to 2019).

We selected all the patients harboring pathogenic gene variants or CNV.

Among them, we identified the patients who experienced both seizures and movement disorders (MDs). We included the following MDs: dystonia, chorea, tremor, myoclonus, parkinsonism, stereotypies, hypomotor paroxysmal attacks, paroxysmal dyskinesias and other non-specified "hyperkinetic abnormal movements". We collected demographic, clinical, neurophysiological and neuroradiological data. We reviewed patients' video documentation.

**Results**: Among 587 patients with pathogenic genetic variants (identified by mutation analysis in 208 cases and by array-CGH in 379), we identified 83 patients whose phenotype was characterized by the association of epilepsy and movement disorder.The genetic spectrum was wide and included variants in the following genes: SLC2A1, PRRT2, ATP1A3, TITF1, TBC1D24, GNAO1, WDR45, PLA2G6, KCNB1, KCNQ2, KCNQ3, HLRC1, DEPDC5, HCN2, SCN1A, SCN2A, SCN8A, SCN9A, DNM1, MEF2C, GLDC, SACS, GPR56, ST3GAL5, CASK, GRIN2A, MTOR. Furthermore, we found several CNV associated to specific genetic syndromes (for example Angelman syndrome or 16p11.2 deletion syndrome) or which included genes likely related to the clinical phenotype (for example PRRT2, SCN2A).

**Conclusions**: Based on clinical features and genetic findings, we identified three groups of patients: the first one included genetic syndromes in which movement disorder and epileptic phenotype were predominant and well defined (for example PRRT2-related paroxysmal dyskinesia associated with benign familial infantile seizures or glucose transporter deficiency syndrome). The other two groups included patients with forms of encephalopathy in which movement disorder and epilepsy were part of a more complex phenotype. Among these, we identified conditions characterized by typical movement disorders (for example parkinsonism in WDR45, dystonic status in GNAO1 or myoclonus in TBC1D24-related disorders) and patients with movement disorders difficult to classify and therefore roughly termed "hyperkinesias".

# P22 - Movement disorders as a leading clinical symptoms in a patient with a RHOBTB2 mutation described in epileptic encephalopathy

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**Introduction:** We present a patient in whom only reanalysis of whole exome sequencing (WES) data allowed to establish an accurate diagnosis - extremely rare hereditary disease that accompanies epileptic encephalopathy and movement disorders.

**Methods:** A 6-year-old girl with hypotonia, scoliosis, dystonic posture of the limbs, atactic gait, multiple choreoathetoid hyperkinesis in the hands (which the mother regarded as epileptic seizures), significant developmental delay and lack of speech was examined. From her 4 mos. she had episodes with fear in the eyes, rapid breathing, adverse of the head and eyes to the side with 1.5-2 minutes duration. According to the results of EEG in the dynamics epileptic activity was never recorded, however, from her 8 mos. she was prescribed carbamazepine, Keppra, Topamax, clonazepam with no effect. At the time the girl underwent brain MRI (Vantage Titan 3Tl (Toshiba), 2016) showed no structural pathology, no pathogenic chromosomal imbalance was detected during molecular karyotyping (GENOSCAN 3000 using SNMP oligonucleotide micromatrix, 2016), while WES (NextSeq 500(Illumina), 2017) revealed a previously undescribed heterozygous mutation in the 53 exon of the HTT gene (chr4:3221975G>A), not correlating with patient phenotype. In our clinic, the girl was carried out continued video EEG monitoring for 22 hours (Nihon Kohden (Japan)), the international system of electrode overlay "10-20" was used with the use of additional electrodes: ECG, EMG (on the deltoid muscles). Reanalysis of WES was also recommended.

**Results:** there were no abnormal activity on EEG, even during stereotypical episodes with tachypnea and movements in the hands, noted by the mother/

A heterozygous mutation in exon 5 of the RHOBTB2 gene (chr8:22865223C>T, rs1554504681) was detected by reanalysis of WES data, resulting in amino acid replacement in the 496 position of the protein (p. Arg496Trp, NM_001160037. 1)

**Conclusions:** a similar de novo heterozygous mutation in exon 8 of the RHOBTB2 gene was identified by Straub et al. (2018) in 2 patients with early infant epileptic encephalopathy, type 64. In this group of patients, in addition to epileptic seizures, severe mental retardation, movement disorders were noted. Totally there were 10 unrelated patients with early infantile epileptic encephalopathy-64 (EIEE64; 618004), founded by Straub et al. (2018) with 5 different de novo heterozygous missense mutations in RHOBTB2 gene. Also 3 patients with acute encephalopathy and febrile epileptic status were described by Belal et al.(2018). Besides there was a poster presented in 2019 by Nicolai et al. in 52nd European Society of Human Genetics Conference describing the debut of acute encephalopathy after a head injury with severe epileptic discharges on EEG and the MRI showed an increment of hippocampal atrophy in a patient with a RHOBTB2 mutation.

So we can assume that here we first describe a child with a mutation in the gene RHOBTB2 with prevailing movement disorders and with normal EEG activity.

# P23 - A case of Early-Infantile Epileptic Encephalopathy associated with compound heterozygosity for mutations in TBC1D24

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**Introduction**: TBC1D24 gene mutations are associated with a wide spectrum of disorders ranging from adult-onset sensorineural deafness (DFNA65) to catastrophic early-onset encephalopathies (EEOE). Most TBC1D24 related disorders show autosomal recessive inheritance pattern, while DFNA65 has an autosomal dominant inheritance. TBC1D24 is a gene mapping on 16p13.3 and coding for a protein containing a Tre2/Bub2/Cdc16 (TBC) domain, shared by Rab GTPase-activating proteins (Rab-GAPs), involved in intracellular vesicles trafficking, axonal outgrowth and oxidative stress resistance.

**Case presentation:** The proband, a ten years old female, is the only child of unaffected parents. The child antenatal and postnatal history was unremarkable until three months of age when the infant presented to the ED of our hospital with myoclonic seizures. There was no family history of seizure disorders. Her mother's history was positive for TIA in adolescent age, her father's medical history was unremarkable. After the first event, myoclonic seizures took place with high frequency and required recurrent admissions to the hospital. Most episodes of myoclonic seizures were segmental, involving the eyelids, the perioral region and the superior limbs. Multiple attempts to obtain pharmacological seizures control had poor results and were complicated by a Steven-Johnson syndrome following the introduction of levetiracetam. Subsequently, the signs of epileptic encephalopathy gradually ensued. The patient never acquired trunk and head control, she has cortical blindness, profound cognitive disability and spastic quadriplegia. The EEG of the child is characterized by diffuse interictal anomalies and disorganized background activity. Brain MRIs showed progressive cortical and subcortical atrophy.

The medical history of the child was also notable for an event of massive superior and inferior vena cava (SVC and IVC respectively) thrombosis when she was three years old. Strikingly, increased activity of all coagulation factors was demonstrated, and she is on warfarin treatment.

CGH array analysis showed a 141kb deletion in 2q21.2 and a 12kb deletion in 12p13.31, but no pathogenetic correlation with epileptic encephalopathies could be made. Further sequencing investigations revealed compound heterozygous missense mutations in the TBC1D24 gene: a Gly110Ser mutation, previously associated with DOORS Syndrome, was transmitted by the father and an undescribed Thr182Met was transmitted by the mother.

**Conclusions:** We describe a case of compound heterozygosity for mutations in TBC1D24 associated with a devastating epileptic encephalopathy. Since the epileptic encephalopathies related to mutations in TBC1D24 are inherited with an autosomal recessive pattern, the newly described Thr182Met mutation is probably crucial in determining the phenotype of the child.

# P24 - PLA2G6, a phenotypic continuum with major clinical implications

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**Introduction**: PLA2G6-associated neurodegeneration (PLAN) is one of the major subtypes of neurodegeneration with brain iron accumulation and comprises a heterogeneous spectrum of age-related phenotypes, with three forms classically recognized: infantile neuroaxonal dystrophy, atypical neuroaxonal dystrophy and dystonia-parkinsonism with onset in early adulthood.

**Objective**: To report on the clinical presentation, imaging features, and the pathogenic homozygous variant identified in the PLA2G6gene in a patient with an atypical neuroaxonal dystrophy. Further the aforementioned classification, PLAN can manifest with intermediate or distinct phenotypes, that we aim to highlight in this work.

**Methods**: We analyzed clinical presentation, imaging features and neurological follow-up of a female infant, born to consanguineous Sephardic Jews parents. A genetic disease have been diagnosticated.

**Results**: The proband of the family had a normal developmental during the first year of life. Initially, by the age of 3, the child started having behavioral concerns, speech difficulties and social communication difficulties. Her gait progressively worsened, with frequent falls and marked motor regression and she sought medical advice at the age of 4.5 years. By the age of 9, the patient had installed a generalized dystonia, a lower limb spasticity, bilateral postural and intentional upper limb tremor. Myoclonus, oculogyric crises and ocular dysmetria have been also noted. During this period, she presented atypical absence-type seizures. Cognitive dysfunction has been progressive over time. Serial magnetic resonance imaging performed at age of 8, 10, 11 and 15 years respectively, showed non-progressive subtle cerebellar atrophy but ptrogressiv iron deposit in basal ganglia, (globus pallidus and substantia nigra) and slightly reduced volumes of optic nerves and chiasm.PLA2G6 homozygous missense amino acid substitution (c.1640A>G, E547G) was documented with appropriate familial segregation (both parents were heterozygotes), thus confirming diagnosis of atypical neuroaxonal dystrophy, At age 15, the patient developed a severe dystonic storm episode with rescue surgical intervention performed for bilateral implantation of the internal globus pallidus and ventral intermediate nuclei of the thalamus. DBS treatment allowed control of the initial Status Dystonicus episode, without recurrent, subsequent episodes. However, currently, at age 20, disorder progressed, clinical presentation including marked, progressive major psychomotor regression, complete anarthria, severe swallowing impairment, pyramidal syndrome with severe spasticity, development of skeletal deformities, residual dystonia, oculogyric crises and a pharmacoresistant epilepsy.

**Conclusions**: We describe a case of atypical PLA2G6, treated with DBS after development of Status Dystonicus. Further disease progression led to development of pharmacoresistant epilepsy. Our case document that phenotype of PLAN is ever expanding. Indeed, atypical PLAN may be more frequent than previously expected. In neurodegenerative disorders such as PLAN, therapeutic strategies remain limited. Our case highlights the importance of neurological follow-up for documentation of phenotype progression. This case suggest that PLA2G6 mutations cause a phenotypic continuum rather than three discrete phenotypes, with major clinical implications.

# P25 - Phenotypic Characteristics of a Mutation in the ADP-Ribosylation Factor Guanine Nucleotide-Exchange Factor 2 (ARFGEF2): A Report of Two Siblings from a Saudi Family

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Mutations in ADP-ribosylation factor guanine nucleotide-exchange factor 2 (ARFGEF2) were first reported in 2004 to cause an autosomal recessive disease characterized by microcephaly and bilateral periventricular nodular heterotopia (BPNH) resulting in severe cognitive delay and early onset seizures. The gene encodes for a large protein called brefeldin A (BFA)-inhibited GEF2 protein (BIG2), which is involved in vesicle and membrane trafficking from the trans-Golgi network (TGN), perhaps explaining the typical phenotype of the disease. Later reports showed that these mutations can also result in movement disorders in association with basal ganglia abnormalities, developmental delays, feeding problems, growth retardation, and cardiomyopathies, expanding our knowledge about the phenotype of this gene mutations. Here, we describe two cases of a boy (15 years old) and his sister (9 years old) from a Saudi family who were diagnosed as having autosomal recessive infantile epileptic encephalopathy with dystonia and global developmental delay. MRI findings were consistent with bilateral signal abnormality of the putamina and bilateral subependymal heterotopia. Genetic analysis showed that both patients were homozygote for c.656dupC, a duplication frame-shift mutation in the ARFGEF2 gene. To date, no specific reports of the phenotype of this specific mutation exist in the literature.

# P26 - De novo deletion of CTNND2 presenting as progressive hyperkinetic movement disorder

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**Introduction**: *CTNND2* gene maps in 5p15.2 region, and it is involved in the regulation of the neuronal migration and functionality of dendrites in mature cortex. This gene is abundantly expressed in the cerebellum in addition to being present in cortical and hippocampal neurons, and a loss of function of *CTNND2* may particularly affect the dendritic architecture of cerebellar Purkinje cells. Missense mutations or deletion in *CTNND2* gene have been reported in patients with severe autism, intellectual disability, and recently associated to familial cortical myoclonic tremor and epilepsy.

**Methods**: We report the case of a patient with a de novo deletion of *CTNND2* presenting with a progressive complex movement disorder, associated with epilepsy, and no cognitive decline.

**Results**: We report an Albanian 6-years old female presenting with childhood-onset and progressive movement disorder firstly affecting the right lower limb, then gradually involving al limbs. No history of fetal distress was reported. This girl's psychomotor development was normal until age two and half. The family observed a progressive hypertonic involvement of all body, with loss of antigravity posture and use of upper arms. The disease has rapidly progressed, and hyperkinetic movement have been exacerbated by acute status dystonicus-like episodic, triggered by concomitant infection or pain experience. The patient had generalized epileptic seizures, not better described, and well controlled by acid valproic treatment. The actual neurological examination documents only a partial head control, without trunk control. The movement disorder is characterized by hyperkinetic movement, involving all body, presenting as intentional tremor and myoclonic movement in the intrinsic feet muscles, and a dystonic component to the lower limbs. During the acute phases, we observe the onset of ballic movements, associated with anxiety and autonomic dysregulation (fever, tachycardia, respiratory change, hypertension, sweating and autonomic instability). The cognitive functions are preserved, the patient has a good interaction using sight, mimics and single words production to communicate.

The pharmacological treatments used have been baclofen, beta-blockers, associated with botuline-toxine injections. Only transitory benefits have been registered using benzodiazepine (delorazepam, clonazepam).

Brain MRI shows slight hyperintensity signals in the semioval centers (left more than right) and in the peritrigonal region. A moderate increment of the liquoral spaces is reported.

SNPs array analysis revealed a deletion in the p15.2 region of the chromosome 5 involving *CTNND2* gene.

**Conclusions**: Neurologic phenotypes previously described to be associated with mutations/deletion of *CTNND2* gene are characterized by intellectual disability or autism or familial cortical myoclonic tremor and epilepsy. We found a deletion involving this gene in a young girl with a complex hyperkinetic movement disorder with a rapidly progressive evolution, associated with acute phases triggered by fever, pain or infection.

# P27 - Combination of chelation therapy and low-manganese diet in a patient with SLC39A14-associated hypermanganesemia and dystonia

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**Introduction:** Mutations in the SLC39A14 gene prevent manganese (Mn) transport into the gut. This causes manganese to build up in the serum, which then is deposited in body tissues (such as bone and the basal ganglia), leading to pathology (bony abnormalities and dystonia). Untreated patients with these mutations develop progressive, treatment resistant dystonia and developmental regression. Published literature suggests that monthly chelation therapy with sodium edetate CaNa2-EDTA can lead to lower serum Mn levels and clinical improvement in dystonia. However in some patients, monthly chelation therapy can be difficult to administer long-term, anecdotally may only transiently reduce Mn serum levels, and may not necessarily lead to clinical improvement. We are attempting to address these issues with a novel protocol which involves not only monthly chelation therapy but a strictly administered, very-low manganese diet.

**Methods:** We initially started chelation treatment according to previously published protocol, using CaNa2-EDTA given monthly over the course of 5 days. After 4 months of chelation treatments, we introduced a gastrostomy tube and initiated a very low Mn diet, in addition to continued monthly chelation therapy. We measured serum, whole blood, urine, and CSF Mn levels at intervals before, during, and after chelation therapy sessions. We periodically evaluated dystonia severity using standardized rating scales, patient videos, parent's report, and physical examination.

**Results:** Although serum manganese levels decreased rapidly as chelation therapy was administered (75->125 (ug/L) pre- to 17.6-21.9 post-chelation), they rose again sharply within 2 days of discontinuing the chelation therapy (69.6-93.4 within 1 week after chelation therapy finished). After initiating the low-manganese diet, the serum manganese levels between chelation therapies did not rise as high (25.6-49.4) and although Mn serum levels did indeed rise after chelation therapy finished the rate of rise was diminished.

**Conclusions:** Monthly chelation therapy may be insufficient to adequately reduce manganese levels in patients with SLC239A14 gene mutations. It is currently unclear whether our protocol of combined monthly chelation and very low Mn diet will ultimately lead to normalization of serum Mn levels, as the patient has over time built up significant deposits of manganese in his body tissues (such as bone). Similarly, it is still too early to determine whether our protocol will lead to meaningful clinical improvement. More data is needed to determine whether this combination of monthly chelation and very low Mn diet results in clinical improvement and lowering CSF Mn levels, but our initial data indicates that this protocol is safe and effective at lowering serum Mn levels.

*Videos available*

*Figure available showing manganese levels over time*

# P28 - A case of DYT1 dystonia initially misdiagnosed as focal epilepsy

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**Introduction**: Dystonia is associated with a number of diseases, but there is often no discrete identifiable pathology in the brain which is regarded as idiopathic. Recent advance in molecular and genetic diagnostic tools has led to the identification of specific etiologies of these idiopathic dystonia. Here, we described a patient with DYT1 dystonia who was initially mistaken for focal epilepsy.

**Clinical report:** A 8-years-old boy visited neurology clinic due to intermittent episodes of dystonic movement of right arm and leg that began several months ago. He was previously healthy and family history was negative for neurological disorders and no other neurologic abnormalities were present. Laboratory tests including complete metabolic profile, thyroid function, magnetic resonance images (MRI) of the brain and spine showed no remarkable abnormality, whereas, electroencephalography revealed several polyspike or spike and slow wave discharges from left frontal areas. With tentative diagnosis of epilepsy, he was treated with antiepileptic drugs but symptoms were getting worse. He developed intermittent dystonic twisting his right hand and foot as well as gait disturbance with right foot inversion and plantar flexion with attaching right arm to his body, which worsened over the course of a day and improved after sleep. With the possibility of dopamine responsive dystonia, GCH1 gene test was done, but no mutation was detected. Subsequent whole exome sequencing revealed c.907_909delGAG mutation for TOR1A gene. Under diagnosis of early-onset primary dystonia, he started to take trihexyphenidyl (antimuscarinic agent).

**Conclusion**: Careful history taking and symptom description is important to diagnose the focal dystonia and exome sequencing is good diagnostic tool to diagnose the genetic dystonia of childhood.

# P29 - GRIN related disorders - an expanding group with epilepsy and movement disorders with a personalized therapy strategy

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**Introduction:** Mutations in NMDA receptors (NMDARs) are an important cause of developmental encephalopathies. The NMDARs are composed of 2 glycine-binding subunits encoded by *GRIN1* and 2 glutamate-binding subunits encoded by *GRIN2A – GRIN2D* genes. GRIN-NDD (neurodevelopmental disorders) are associated with various clinical signs, including epilepsy/movement disorders. Clinical features vary depending on the NMDAR's subunit and structural domain affected, resulting from gain- and loss-of-function mutations. Recently, a strategy for personalized treatment has been developed at the Barcelona GRINpathies' team. Additionally, a worldwide registry based on the I-NTD platform has started. **Objective**: To increase awareness in this emergent and rapidly expanding group of developmental encephalopathies. To describe the different epilepsy/movement disorders in GRIN-NDD.

**Methods:** Literature review of movement disorders (MDs) and epilepsy spectrum profiles of individuals with GRIN-NDD reported since 2010 to date.

**Results:** The phenotypic spectrum of **GRIN1-NDD** is associated with mild-to-severe global development delay (GDD), the presence of dystonic, dyskinesia and chorea in half of the patients, epilepsy in 65% (onset from birth to 11-year-old) and oculogyric crisis in a small percentage. **GRIN2A-NDD** display the most recognizable and broad epilepsy spectrum, comprising early-onset epileptic encephalopathy, rolandic epilepsy, benign epilepsy with centrotemporal spikes, continuous spike-and-waves during slow-wave sleep, and Landau-Kleffner syndrome. Ataxia, dystonic/spastic/choreatic MDs have been identified so far, in a few cases. Cognitive impairment is inconstant. **GRIN2B-NDD** shows GDD and some of them with dystonic/dyskinetic/choreiform movements presenting in infancy or childhood. Epilepsy (50%) starts between birth and 9 years old, some with severe form leading with a stagnation or even development decline (West Syndrome (WS) or Lennox-Gastaut syndrome). Seizures may be generalized mostly tonic or tonic-clonic, focal and also epileptic spasms (hypsarrhythmia fulfilling WS criteria). Regarding treatment, a recent publication shows developmental improvement from L-serine supplementation in a patient with GRIN2B loss-of-function variant.

**Conclusions:** GRIN-NDD should be considered in patients with MDs and epilepsy, with or without cognitive impairment, in cases of probable genetic etiology. Despite the overlapping spectrum, the epilepsy profile can be an important clue to distinguish between GRIN-NDD. Further clinical characterization of this group of disorders is needed. An international registry, that has just started, could contribute to a better knowledge of these aspects. A strategy for personalized treatment and L-serine clinical trial is going on.

(*) the first two authors contributed equally to this work.

# P30 - ATP1A3-related epilepsy: report of seven cases and literature-based analysis of treatment response

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**Introduction**: ATP1A3 related disease is a clinically heterogeneous condition currently classified as alternating hemiplegia of childhood, rapid-onset dystonia-parkinsonism and cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss. In recent years, it has become apparent that a remarkably large subgroup is suffering from often difficult-to-treat epilepsy. The aim of the present study was to assess the prevalence and efficacy of commonly used anti-epileptic-drugs (AEDs) in patients with ATP1A3 related seizures.

**Methods**: Retrospective study of patients in combination with a systematic literature-based review. Inclusion criteria: verified ATP1A3 mutation, seizures and information about AED treatment.

**Results**: The literature review yielded records for 188 epileptic ATP1A3 patients. For 14/188 cases, information about anti-epileptic treatment was available. Combined with seven unpublished records of ATP1A3 patients, a sample size of 21 patients was reached. Most used AED were levetiracetam (n=9), phenobarbital (n=8), valproic acid (n=7), and topiramate (n=5). Seizure reduction was reported for 57% of patients (n=12). No individual AEDs used (either alone or in combination) had a success rate over 50%. There was no significant difference in the response rate between various AEDs. Ketogenic diet was effective in 2/4 patients. 43% of patients (n=9) did not show any seizure relief.

**Conclusions**: Epilepsy is a significant clinical issue in ATP1A3 patients, but only a minority of publications provide any information about patients' anti-epileptic treatment. The findings of treatment effectiveness in only 57% (or even lower) of patients, and the non-existence of a clear first-line AED in ATP1A3 related epilepsy stresses the need for further research.

# P31 - The expanded phenotypic spectrum of BRAT1 gene mutations: a new compound heterozygous case

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**Introduction**: BRAT1 encoding BRCA1-associated ATM activator 1 is a gene implicated in the DNA damage pathway, by the ATM's autophosphorylation. Homozygous or heterozygous loss of function mutations of BRAT1 gene, determine a reduction in the cellular proliferation and an alteration in the mitochondrial homeostasis, causing neuronal depletion and cerebral atrophy. The phenotypic spectrum associated with BRAT1 mutations, to date described in 21 patients, encompass a wide range of clinical phenotypes, from lethal neonatal syndrome with rigidity and multifocal seizures (RMFSL; OMIM #614498) to milder forms with neurodevelopmental disorder and cerebellar atrophy with or without seizures (NEDCAS; OMIM #618056). We expand the phenotypic spectrum of BRAT1 related disorders reporting an 18 years old girl with compound heterozygous variants presenting with myoclonic seizures and slight cerebellar symptoms associated with cerebellar atrophy, in the context of a typical neurodevelopment history and normal intellectual functioning.

**Methods**: The genetic profile was investigated by a clinical exome sequencing (Illumina Nextera Trusight One kit on platform Illumina Miseq Dx) and the gene transcripts have been confirmed by Sanger sequencing in both the proband and parents, with the subsequent dosage of the RNA transcripts.

**Results**: A compound heterozygous variant on BRATI gene was detected: c.638_639insA (p.Val214GlyfsTer189) and c.1395G>A (p.Thr465). Segregation was confirmed in the parents. Only the c.638_639insA (p.Val214GlyfsTer189) mutation has been previously described in the severe form of RMFSL, while the pathogenic variant c.1395G>A (p.Thr465), determining the exon 9 skipping in the BRAT1 gene, has never been reported before. The moderate phenotype of our patient was characterized, at the age of 18, by a normal cognitive development, with a regular academic career. Previously, she was referred for the onset of myoclonic seizures (eyes blinking; upper limbs jerks) at the age of 13, presenting paroxysmal epileptic activities at the electroencephalographic studies, increased by the activation procedures (hyperpnoea; photic stimulation) and not well responding to the pharmacologic treatment (Valproic Acid; Levetiracetam, Lamotrigine). The neuroimaging studies (MRI; MRS), during the follow-ups, revealed nonprogressive cerebellar atrophy with a reduction in the lactate and in the N-acetyl aspartate peaks. At the neurological examination, impairment in the static and dynamic balance was observed and a slight tremor.

**Conclusions**: This case expand the phenotypic spectrum of BRAT1 mutations, to date restricted to RMFSL and NEDCAS phenotypes, to include slight ataxic syndromes with nonprogressive cerebellar atrophy and epilepsy in absence of a neurodevelopmental disorder.

# P32 - A Rare Case of Infantile Spasm: An Unexpected Mutation

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**Introduction**: The KCND2 gene codes for the α subunit of potassium channel Kv4.2, voltage-gated, shal-related subfamily. These channels are important for normal action potential function, especially the repolarization phase. They activate at sub-threshold membrane potentials, inactivate rapidly, and quickly recover from inactivation and regulate dendritic excitability by attenuating back-propagating action potentials.

**Case**: We report a case of a 2 years old boy who presented initially with infantile spasms. He started to have flexor spasms at the age of 6 months, which were more frequent upon awakening from sleep. Then at the age of 9 months, his EEG showed hypsarrthmia. Brain MRI showed delayed myelination. He was started on vigabatrin, at an outside hospital but with poor response, later his spasm disappeared after initiating prednisolone therapy (8 mg/kg/day). Later on, at the age of 2 years, he was referred to our intuition, KFSH&RC, presenting with new seizure semiology of generalized tonic-clonic seizure associated with multiple ICU admissions for status epilepticus. At our institute, genetic testing with epilepsy panel was performed and was positive for SCN1A gene, traditionally associated with Dravet Syndrome. However, upon filtering his variant through the Saudi Genome database, it was found to be a variant reported in the normal Saudi population. Trio whole exome sequencing was performed and was positive for a de novo KCND2 mutation (c.1208C>G:p.P403R) in the patient's case. This was a De novo mutation as both parents were negative for it. This mutation was previously reported only once, in a twin couple diagnosed with autism associated with intractable epilepsy. To our knowledge, this is the first report characterizing the genotype-phenotype of a Saudi case of infantile spasms with a KCND2 mutation.

# P33 - Bilateral striatal lesions, coreoathetosis and epilepsy: possible association with a PDE10A variant

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**Introduction**: Description of a clinical case currently 2 year old boy admitted at 11 months with global developmental delay, choreoathetoid, dystonic and oculogyric movements, epilepsy and microcephaly possibly associated with a variant in gene PDE10A c.14C>T, a not previously described genetic mutation causing bilateral striatal necrosis of pallidus nuclei.

**Methods**: Description of clinical, radiological and laboratory findings of the case.

**Results**: 11 month old boy, first child born of non consanguineous parents with background of global developmental delay and hypoactivity admitted with acute choreaoathetoid movement disorder and oculogyric crisis associated with encephalopathy. EEG showed non convulsive status epilepticus.

Extensive studies for infectious, inflammatory and autoinmune causes including studies of anti-neuronal antibodies and anti-dopamine receptor antibodies resulted all negative. MRI Head showed remarkable bilateral striatal necrosis of pallidus nuclei. Metabolic studies revealed high lactate in CSF 2.48 mmol/dl (nv up to 2.2) associated with a peak of lactate in pallidus nuclei in Head MRI spectroscopy. CSF Neurotransmitters were normal. Fibroblast studies for PDH were negative along with other metabolic studies.

**Extense genetic studies:** Whole exome sequencing, Mitochondrial genoma sequencing studies (Cento Mito Geno) were all negative.

Amplified gene studies for epilepsy, nigro-striated degeneration disorders and Aicardi Goutieres were performed and showed a variant in gene PDE10A with c.14C>T;p. (Pro5Leu) of uncertain significance (according to ACMG) with very low frequency argument in favor of its harmful effect. This variant is related with IOLOD sydrome (dyskinesia, limb and orofacial, infantile onset).

On admission he was treated with Clonacepam, IV Methylprednisolone and mitocondrial cofactors with resolution of non convulsive epileptic status and improvement in intensity of the hyperkinetic disorder without a complete resolution of it.

Treatment with L-Dopa was started because we think AMP cyclic is very important in the release of dopamine with a discrete clinical improvement. Levetiracetam was weaned and was started on Lamotrigine. He is currently two 2 years old now and achieving good head control, sitting with support and starting eye pursuit.

**Conclusions**: Bilateral neostriatal necrosis (BSN) and other striatal lesions (LS) are associated with movement disorders and can be observed in a very large number of neurological conditions of acquired and hereditary metabolic or genetic origin.

# P34 - Hyperekplexia in patient with GNAO1-related syndrome.

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**Introduction**: The phenotypic spectrum of GNAO1-related neurodevelopmental disease includes early onset epileptic encephalopathy and a range of movement disorders with or without epilepsy. Movement disorders consist of a severe early-onset hyperkinetic syndrome (chorea, dystonia or orofacial dyskinesia). In most cases movement disorders fluctuate and are poorly responsive to medical therapy. Most of the patients with GNAO1-related syndromes are hypotonic and have developmental delay ranging from mild to severe. Hyperekplexia (pronounced startle responses to tactile or acoustic stimuli and hypertonia) is not characteristic symptom of GNAO-related syndromes.

Our objective is to report a case of 7-year-old girl with severe hyperekplexia and GNAO1-related syndrome.

**Methods**: 7-year old girl was born to non-consanguineous patients after uncomplicated premature birth. She was referred to our hospital because of epilepsy with rare seizures and psychomotor developmental delay. First seizure in our patient appeared in second week of age. Startle responses started from 3 years of age. Frequency of startle response fluctuated. In some periods the symptoms appeared many times a day, even after a slight acoustic stimulus like the sound of the car outside the window.

In neurological examination she showed generalized hypotonia and involuntary movements of the face and limbs more prominent in the upper extremities (chorea). Occasional dystonic features (cervical dystonia) were seen. During hospitalization we observed multiple pronounced startle responses. Firstly we suspect reflex epilepsy. We made electroencephalography, registering the startle response, but we did not find any elektophysiological and clinical correlation.

**Results**: Whole-exome sequencing revealed de novo mutation in GNAO1 gene (the gain-of-function, c.607G>A). In our patient early onset focal epilepsy, developmental delay, hypotonia and movement disorders coexists with further development of hyperekplexia.

**Conclusions**: Hyperekplexia can be one of the symptom in GNAO-related neurodevelopmental disesase.

# P35 - Movement Disorder Childhood Rating Scale for clinical management and follow up in FOXG1 related syndrome

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**Introduction**: FOXG1-related syndrome is a rare neurodevelopmental encephalopathy characterized by developmental delays, early-onset dyskinetic movement disorders, epilepsy, autism like traits, microcephaly, absence of language, severe cognitive impairment, stereotypic hand movements, and corpus callosum dysgenesis. Early-onset hyperkinetic movement disorders, such as choreoathetosis and orolingual/facial dyskinesias, which are usually non-responsive to medication, are the hallmarks of this disease. This syndrome is associated with heterozygous variants in the forkhead box G1 (FOXG1) gene, a transcription factor that is critical for forebrain development, where it promotes progenitor proliferation and suppresses premature neurogenesis. There are two clinical syndromes recognized in FOXG1, deletions/intragenic loss-of-function mutations and duplications. Each of these has distinct developmental and behavioural characteristics. Individuals with deletions or intragenic mutations of FOXG1 have a more severe clinical features and the epilepsy and the movement disorders in them are refractory to treatments. Epilepsy is very common in these children, with polymorphic seizures developing early in childhood (focal, myoclonic and generalized tonic-clonic seizures). The movement disorders are present in all patients: chorea/athetosis, orolingual/facial dyskinesias and dystonia are the most frequently present. Stereotypies, tremor and tics can be present and commonly involved the upper limbs with mouthing of toys, grasping clothes/objects, nail biting and midline wringing. Myoclonus and dystonia are both present in 24%. Pyramidal features are also commonly reported, and many patients are noted to have axial/peripheral hypotonia, brisk deep tendon reflexes, upgoing plantar responses and ankle clonus. Others problems reported in these patients are sleep dysfunction, as result of frequent awakenings, and gastrointestinal disturbances such as gastroesophageal reflux and dysphagia that sometimes requiring surgical treatment with a fundoplication and feeding tube placement.

**Methods**: in this study we evaluated a cohort of 5 children affected by FOXG1-related syndrome (deletions or intragenic mutations). The average age at diagnosis were 4,5 years (SD ±5,4). All patient presented onset of epilepsy before 1 year (mean 7,2 months) and movement disorders before 2 years (mean 12 months). 4 of them were treated with anticholinergic drug (trihexyphenidyl) or tetrabenazine. The participants were evaluated using MD-CRS 0–3 or MD-CRS 4–18 R at baseline, before starting pharmacological treatment (T0), after 6 (T1) and 12 months (T2) of treatment in order to verify the responsiveness of the MD CRS also in FOXG1 related syndrome. The study analyses the scale responsiveness for the three indexes (e.g. Index I, Index II and Global Index) in each group with time (T0, T1 and T2).

**Results**: significant differences were found between time points for all indexes, in particularly in the evaluation of severity. This confirm our previous result that the MD-CRS is a suitable scale for identifying severity of movement disorders also in individual affected by FOXG1 related syndrome.

**Conclusions**: this study suggest that MD CRS 0-3 and 4-18 R is useful to detect changes and evaluate the responsiveness to the oral pharmacological therapy and confirm that is a standardized outcome measure for movement disorders in developmental age.

# P36 - Bardet–Biedl syndrome with Seizures: A Novel Mutation Report

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**Background:** Bardet–Biedl syndrome (BBS) is a genetically heterogeneous, ciliopathy disorder characterized primarily by retinal dystrophy, obesity, hypogonadism, renal abnormalities polydactyly, and mental retardation. Several rare gene mutations have been identified to be associated with BBS in recent years, amongst is BBS8 mutations which are reported in very few families around the world. BBS8 codes the centrosomal and basal body protein TTC8, found in ciliated neurons, and which contains several tetratricopeptide repeats important for protein-protein interactions in such neurons. Rarely is BBS associated with the development of seizures.

**Case**: We report a case of a 13 months old Saudi male child who was diagnosed with BBS at KFSH&RC. He suffered several classical BBS features including congenital heart disease, chronic kidney disease stage III, congenital liver disease, polydactyly and syndactyly, ambiguous genitalia, recurrent chocking and aspiration requiring multiple PICU admissions. At the age of 12 months, he developed multiple attacks of new-onset seizures, the first of which was following a febrile illness he suffered. His seizures were in the form of head deviation to the right side with up rolling of the eyes that were followed by general tonic-clonic seizures. They were not associated with cyanosis initially but progressed to exhibit perioral cyanosis in later attacks. His attacks lasted anywhere between few seconds and 10 mins before resolving spontaneously. Examination was normal except for axial hypotonia. His parents are consanguineous and have one healthy sibling. Both parents are healthy but his family history is positive for febrile seizures from the maternal side. Upon investigating him, his EEG showed multifocal epileptiform discharges, most prominently seen left posterior temporal area and continuous generalized slow activity with rare intermittent brief generalized attenuations. His CT scan showed no evidence of acute intracranial abnormality. His MRI showed mild brain parenchymal volume loss with myelination delay and reduced white matter volume, best illustrated by thinning of the corpus callosum. Interestingly, his gene testing releveled a novel, autosomal recessive, homozygous, missense mutation in the gene coding for TTC8 (exon 7:c.107 G>A:p.C36Y). His seizures were controlled by carbamazepine and clobazam. Up to our knowledge, this mutation has never been reported previously in BBS patients as previous BBS cases presenting with seizures were mainly limited to BBS1 mutations.

# P37 - Movement disorders in PIGA-related DEE

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**Introduction**: PIGA germline mutations have been associated with early onset developmental and epileptic encephalopathy (DEE). The phenotype is characterized by onset of seizures during first months of life, developmental delay, and other organ abnormalities such as cleft palate, cardiac anomalies and vescico-ureteral reflux. Our aim is to report two patients with PIGA-related DEE, focusing on movement disorders.

**Methods**: We reviewed clinical, genetic, neurophysiological, and neuroimaging data. Video-EEG recordings were reviewed in order to characterize seizure semiology and movement disorders.

**Results**: The first patient is a 3 year old boy, carrying a genetic variant in PIGA gene (p.Arg119Gln), inherited from his healthy mother. Epilepsy onset was at the age of two months. Seizures were focal mainly arising from central and temporal regions, migrating from one hemisphere to the contralateral. Interictal EEGs revealed slowed background activity, and rare bilateral temporal epileptic discharges. Since the beginning of seizures he presented also with diskinetic movements of upper and lower limbs. Diskinesia were mainly asymmetric and asynchronous and almost continuous during wakefulness, disappearing during sleep. At last follow-up evalutation, at the age of 3 years, he presents with multiple per day epileptic seizures, profound motor and cognitive delay and diskinetic movements. He has a severe hypotonia with no head control. The second patient is a 5 years old boy with a de novo PIGA genetic variant (p.Ala135Val). He was delayed since birth. Epilepsy started at 8 months of age with bilateral focal seizures. Also he had a profound hypotonia and diskinetic movements of upper and lower limbs. Differently from the other patient, at last follow-up, the second patient acquired minimal developmental skills (walking with support), and dyskinesia disappeared. Seizures are monthly.

**Conclusions**: Movement disorders in patients with PIGA-DEE are not characterized. We report diskinetic movements in two patients in order to highlight this feature. This specific feature might be relevant also for early identification of genetic etiology.

# P38 - Neuropsychological evaluation in GNAO1 encephalopathy using eye tracker

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**Introduction:** *GNAO1* is a gene coding for the subunit α of the guanosine nucleotide-binding protein G(o) and is associated with a neurodevelopmental disorder characterized by two main phenotype (a) developmental delay with pronominally epileptic encephalopathy phenotype or (b) movement disorder main phenotype. It is well known that *GNAO1* encephalopathies are associated with developmental delay. However so far, to the best of our knowledge, little is known about cognitive or communication level and this is the first structured neuropsychological evaluation performed.

**Methods:** We evaluated the neuropsychological phenotype of 4 patients with GNAO1 mutations. M:F ratio was 2:2. Median age at evaluation was 6.2 years old ranging from 3 to to 14 years old.

All patients were clinically stratified with Gross Motor Function Classification System (GMFCS), Manual Ability Classification System (MACS) and Communication Function Classification System (CFCS) grading from I to V. Dystonia was assessed with the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) ranging from a severity score of 0 to 120. A comprehensive neuropsychological evaluation was conducted with the Adaptive Behavior Assessment Systems (ABAS) to assess the adaptive skills, the child behavior check list (CBCL) to screen for neuropsychiatric comorbidity, the Pediatric Quality of Life Inventory (PedsQ) to assess the quality of life, and the Parent Stress Inventory (PSI) to asses parental stress. Using an eye tracker (Sprout Hp ®) we performed a non-verbal cognitive assessment with Raven's Progressive Matrices (either SPM or CPM according to age). Moreover, a language evaluation using the Italian test (TFL Test Fono Lessicale) to evaluate both Receptive and whenever possible Expressive Language.

**Results:** 4/4 had a gross motor score of V at the GMFCS, 3/4 had manual ability score of IV and 2/4 of V at the MACS and 3/4 had a communication score of IV and 1/4 of V at the CFCS. Adaptive skills were below 2 standard deviation from mean in all patients and parent stress was above 75% in all patients ranging from 75 to 90% with a mean stress index of 84%. Quality of life was globally reduced in all patients. All patients had hypotonia and developmental delay. 1/4 had epilepsy, and all (4/4) had movement disorders, including dystonia and dyskinesia. Median score at BFMDRS was 42.5 ranging from 16 to 84. All the patients showed an excellent intentional communication 2/4 patients completed the cognitive test and answered respectively to 23 and 24 items. All patients completed the receptive language with a mean scoring of 29,5/45, ranging from 24 to 33 correct answers. None of the patients was able to perform the productive language test scoring indeed 0/45.

**Conclusions:** We have demonstrated that through an eye tracker we were able to evaluate the cognitive and communication level in a cohort of children with important impairments in speech production and motor disability, otherwise impossible to be tested. This is an important goal both for individual rehabilitation of the children and for research on neuropsychology in GNAO1 encephalopathy. Future prospective, currently ongoing, is to use the eye tracker as a rehabilitation tool to implement the communication ability and ameliorate the inclusion and the socialization of GNAO1 children and to perform serial follow ups to evaluate the trend of cognitive and language profile.