RÉSUMÉS

Abstracts

CO 01

EXPANDING THE SPECTRUM OF PORETTI-BOLTSHAUSER SYNDROME: TEN NEW PATIENTS WITH LAMA1 MUTATIONS

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Background: Described in 2014, Poretti-Boltshauser syndrome (PTBHS) combines delayed motor development, DI, oculomotor apraxia, severe myopia and cerebellar dysplasia with cysts. This disorder is linked to recessive mutations of LAMA1 gene that codes one of the subunits of laminins, a major protein component of the basal membrane.

Methods: We describe ten unrelated patients with cerebellar dysplasia, initially referred for Joubert syndrome or dystroglycanopathy due to the presence of cerebellar cysts, in whom we identified biallelic LAMA1 mutations by NGS.

Results: At the last follow-up, these children were between the ages of 3,7 and 18. The first symptoms were noticed before the age of 4 months. These infants appeared visually impaired with poor visual fixation and pursuit and had hypotonia. Ocular motor apraxia became obvious in 9 patients once they achieved head control and abnormal smooth tracking was report in the last patient. All had a delay in motor acquisitions with a non-progressive ataxia (autonomous walking acquired between 18 to 48 months). Myopia was present in 9 patients, severe in 5. Nystagmus (2), strabismus (4), retinal abnormalities (2) and optic atrophy (2) were also noticed. In addition to these previously reported clinico-radiological characteristics, we observed new features in these patients. Two patients had hydrocephalus and 1 severe ventriculomegaly; 1 patient had an occipital cephalocele and 1 an occipital cutis aplasia suggesting a cranial dysraphism; and 4 of them had a dysmorphic tectum. Moreover, prenatal ultrasonography detected a ventriculomegaly in 3 patients with an abnormal cerebellar vermis in one, while until now no prenatal abnormalities were reported in PTBHS. It is important to underline, that IQ was in normal range but heterogeneous in 3 patients and that 9 children were attending normal school with rehabilitation and 1 special school for visually impaired children.

Conclusions: Our findings enlarge the spectrum of structural defects due to biallelic LAMA1 mutations. Interestingly, as cerebellar cysts, hydrocephalus, tectal dysplasia and occipital cephalocele are reported in dystroglycanopathies and in children with other laminins mutations (LAMB1, LAMC1 and LAMB2). In addition, prenatal ultrasonography may detect ventriculomegaly and cerebellar dysplasia in these patients, but not cerebellar cysts. Concerning prognosis, all of these patients acquired autonomous walking, despite cognitive difficulties they can most often be schooled normally, even if some are visually impaired.

CO 02

DESIGN, BASELINE CHARACTERISTICS, AND 2-YEAR FOLLOW-UP FROM THE MPS IIIA NATURAL HISTORY STUDY USED AS CONTROL GROUP IN GENE THERAPY TRIAL

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Objectifs: Mucopolysaccharidosis type IIIA (MPSIIIA) (OMIM 252900) leads to infantile-onset neurodegeneration and early death. To reinforce published data on the natural history of MPS IIIA and expand the geographic outreach, Lysogene launched an observational study in five countries (NCT02746341). This study will function as a non-concurrent control for the Phase 2-3 gene therapy trial (NCT03612869).

Contenu: Lysogene coordinated discussions with experts ensuring that the selection of parameters measured in the NHS and the gene therapy trial are robust and clinically meaningful. This NHS is perfectly compliant to the International MPS Consensus for Cognitive Endpoints recommendations (van der Lee, 2017).The NHS study enrolled twenty-three patients, less than 9 years of age, with the classical form of MPS IIIA. Subjects are from Brazil, France, Germany, Netherlands and UK. Median age at enrolment was 61 months (range, 28 to 105). Median age at diagnosis was 37 months. Baseline data showed a mean BSID-III development age (DA) of 15.2 months (range, 4.67 to 29) with mean developmental quotient (DQ) score of 31.52 (n=23). At six months the mean DQ score was 30.52 (n=20) and at twelve months the mean score was 25.71 (n=19). While DA increased slightly at 6 and 12 months (8.58% and 3.35%, respectively), DQ declined by 2.33% and 17.72% at 6 and 12 months, respectively. At baseline, the mean DA as measured by the VABS-II was 19.32 months. Most patients showed decline in VABS-II DA and DQ scores over 12-months. Mean VABS-II DQ were slightly higher than mean BSID DQ scores but correlate in terms of decline –0.84% and -14.07% at 6 and 12 months, respectively.

Conclusion: This NHS forms the largest international cohort in MPS IIIA. The use of consensually agreed outcome measures and instruments for patient evaluation allows data pooling with other studies using the same assessment tools and quality standards. The Lysogene gene therapy phase 2-3 trial will recruit 20 patients in Europe and the US through 2019. The primary objective will be to assess the drug efficacy in improving or stabilizing the neurodevelopmental status of patients compared to the expected evolution based on the above natural history data.

CO 03

AUTISM SPECTRUM DISORDER (ASD) IN REUNION ISLAND: RELATIONSHIP BETWEEN SOCIAL AND ECONOMIC CONDITIONS AND ASD INTENSITY

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Introduction: Autism includes a spectrum of various disorders, evolving differently fromone subject to another, according to identified individual factors and not very well-known environmental ones. Existing longitudinal studies research the influence of therapeutic interventions. Our study aims to find a relationship between the intensity of the disorder and the Social and Economic Environment of the child.

Method : Our cross-sectional and analytical study was based on a prospective sociometric Survey with parents of children aged from 5 to 12 years old, diagnosed with ASD atCRA Réunion/Mayotte from 2007 to 2017. The results were related to the retrospectiveevaluation data (ADOS, language level, intelligence quotient).

Results: 97 parents answered the survey. The results confirmed that autism affects all social classes. They showed a significant relationship between the intensity of the disorder and the level of education and the socio professional category of the father, but none concerning the mother. A significant link with the household's average income level was also revealed. Thus, the higher the income level of the household, the lower the intellectual and language deficit, and the lower the score obtained at ADOS.

Conclusion: This study suggests the influence of social and economic factors on the intensity of autism, with a more intense intellectual and language deficit among disadvantaged social categories. However, our study was geographically restricted to a single department (Reunion Island), and to a limited number of 97 parental responses. These results motivate other studies or large-scale follow-up to confirm or refute this influence of the social and economic environment. Our results raise the issue of social inequalities in health and accessibility to care that may influence the national policy of care for autism.

CO 04

LANGAGE ET MOTRICITE DU PREMATURE : EFFET D'UNE REEDUCATION PROTOCOLISEE

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Objectifs : Evaluer l'effet d'une rééducation protocolisée courte sur les enfants nés grands prématurés à l'âge de 3 ans

40% de difficultés neuromotrices sont rapportées chez les grands prématurés de moins de 32 sa. L'étude Epipage rapporte un taux de paralysie cérébrale en diminution (9 à 6%) mais des difficultés neurologiques mineures et d'échec scolaire en augmentation. Les difficultés neurocognitives sont multiples, dyspraxie visuospatiale, trouble d'attention, trouble du langage. Ce dernier est assez peu décrit dans la littérature et souvent considéré en lien avec un déficit cognitif global. Les évaluations cognitives des prématurés sont très souvent normales dans l'étude EPIPAGE. Le langage oral est fondamental pour le langage écrit et les apprentissages scolaires. Il suit un développement maturatif précis selon des étapes sensori motrices.

Nous émettons l'hypothèse que les troubles sensorimoteurs mineurs peuvent modifier précocement et structurellement le langage oral notamment la phonologie. L'évaluation précise des composants du langage, sa stimulation spécifique, courte et précoce peut-elle modifier le développement du langage avant la fin de la fenêtre développementale.

Contenu : Etude multicentrique, au sein d'un PHRC national, randomisée en double aveugle.552 enfants ont été inclus sur des critères de prématurités sans paralysie cérébrale ni déficience intellectuelle ni trouble sensoriel avéré.165 enfants nés grands prématurés ont été randomisés. 78 dans un bras sans rééducation 87 dans un bras avec rééducation pendant 6 mois le critère de jugement principal est la phonologie, les critères de jugements secondaires sont la morphosyntaxe et la compréhension.

Conclusion : La rééducation "Dire et Faire" associant un protocole de ralenti imité et d'attention visuelle améliore significativement les composants du langage 6 mois après dans le groupe des enfants rééduqués comparativement au groupe non rééduqué.

CO 05

SOCIAL COGNITION IN CHILDREN AUTISM SPECTRUM DISORDERS: AN EYE TRACKING STUDY

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BACKGROUND: Autism Spectrum Disorders (ASD) is characterized by impairment in social interaction and communication, restricted, repetitive and stereotyped patterns of behaviors or interests. ASD individuals show diminished orientation towards faces and deficits in face recognition. Recently, by using the Face-n-Food paradigm, it had been shown that ASD individuals exhibit deficient face tuning in face-like non-face images (Pavlova et al., Sci Report 2017). For better understanding of the origins of this deficit, we implemented eye tracking methodology.

METHODS: Sixteen individuals (mean age: 14.1 years, 15 males) affected by ASD were enrolled in the study. Face tuning was studied by using Face-n-Food paradigm, a set of ten food-plate images similar with the Giuseppe Arcimboldo style. The images were proposed in a specific order from the last to most resembling a face. Gaze behavior (in terms of percentage of fixation, time spent and gaze map in the areas of interest such as mouth, eyes and outside the face) was recorded by using eye tracking technology during the Face-n-Food stimuli presentation. Data set of 16 typically developed individuals matched by age and gender were used for comparison.

RESULTS: Using eye tracker device, we observed that the percentage of visual fixation on external "face" for each food-plate image is higher in participants with ASD than control group: fixation varies from 10 to 28% in subjects with ASD and from 4 to 12% in healthy controls ($p < 0.01$, Wilcoxon-Mann-Whitney test, two sided). The mean percentage of time spent on area outside the "face" for each food-plate image is significantly higher in subjects affected by ASD than typically developed individuals (8 to 26% in ASD versus 5 to 11% in healthy individuals). The mean percentage of fixation and the mean percentage of time spent on social relevant area (mouth, left eye and right eye) are higher in control group.

CONCLUSION: Individuals with ASD are not only less sensitive to faces in non-face images, but their gazing differs substantially from typically developing controls. In particular ADS children seem to focus visual fixation outside the face compared to control group probably because visual attention in ASD individuals was most impaired when stimuli had a high social content.

CO 06

ENVIRONMENTAL ADAPTATION AND EARLY VISUAL TRAINING TO PROMOTE NEURODEVELOPMENT IN INFANTS WITH VISUAL IMPAIRMENT: A PILOT STUDY

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Objectifs: Systematic reviews on early visual intervention in infants reported promising but inconclusive results due to extreme among programs, lack of control group and random allocation. Our aim is to evaluate the effects of environmental adaptation and early visual training in visually impaired infants and to test whether this approach lead to changes in the overall neurodevelopment.

Contenu: Thirty infants (average age: 5.9 mths, 16 males) with visual impairment of cerebral and peripheral origin associated with neurological signs/ developmental delay received a visual training for a 6 months period based on environmental modification and training on oculomotor functions and hand-eye coordination. Thirty infants (average age 6 mths, 18 males) matched by gestational/chronological age, sex, diagnosis and psychomotor abilities were recruited as control group. Neurovisual abilities were primary outcome measures; developmental quotient and subscales of Griffiths-ER were secondary ones. Assessments were carried out at baseline and after 6 months of treatment by a child neurologist blind to group assignment. At baseline the two groups did no differ on demographic and clinical variables ($p > 0.5$ for all). After 6 months, oculomotor functions improved in both the groups (fixation, smooth pursuit and saccades $p<0.01$). Improvement in all the oculomotor components was better in the treated group ($p<0.01$). Visual acuity and contrast sensitivity ameliorated in both the two groups ($p<0.01$). Visual acuity better improved in the treated group ($p<0.01$). At Griffiths Scales Hand-Eye coordination and Performances sub-quotients ($p<0.01$) improved in the treated group. Developmental Quotient ($p<0.01$), Language ($p<0.01$), Hand Eye Coordination ($p=0.02$) and Performance ($p<0.01$) sub-quotients decreased in control group.

Conclusion: Environmental adaptation and early visual training seem to influence favorably visual abilities, vision-related performances and the overall neurodevelopment outcome in infants with visual and neurodevelopmental impairments.

CO 07

NATURAL HISTORY IN LEUKODYSTROPHIES RELATED TO POLR3A AND POLR3B MUTATIONS: A MULTI-CENTRIC SURVEY OF 21 PEDIATRIC CASES

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Objectifs: POLR3-related leukodystrophy is a hypomyelinating leukodystrophy caused by mutation in POLR3A and POLR3B genes, encoding respectively the first and second largest subunit of the RNA polymerase III complex. The objective of this study is to summarize the clinical features of these conditions and to evaluate if it is possible to identify different phenotypes and disease progression for different genotypes.

Contenu: A retrospective cohort study was performed including 21 patients with POLR3 related leukodystrophy, referred to CRMR Leukofrance. 6 patients with POLR3B and 15 with POLR3A mutations from 11 different hospitals were enrolled. An earlier onset of the disease was observed in patients with POLR3B mutations compared to POLR3A (50% motor delays compared to 27%, onset at 1.5 years vs. 3.8 years). Progressive ataxia was present in 53% of POLR3A vs 17% of POLR3B, whereas hypotonia and delayed acquisition from the first months of life were more frequent in POLR3B (33% vs 6.7%). During evolution, spasticity, dystonia, swallowing disorders and vescico-sphincterian disorders were more frequently observed in POLR3A mutated patients. The non-neurological manifestations of this pathology are present in the 2 groups without significant differences. MRI analysis showed a higher frequency of diffuse hypomyelinization in POLR3B patients, whereas POLR3A patients have preserved more frequently myelinization in the early myelinated regions.

Conclusion: These data seem to underline that when the pathology is induced by mutations in POLR3B gene, it presents a more precocious onset and half of the patients show a pattern of disease evolution more similar to a neurodevelopmental disorder, at a first stage with an abnormal development and then presenting a second phase of stagnation and a third one of degradation. On the contrary, in the disease related to POLR3A gene we find more often a normal neurological development with a later onset of neurological signs and symptoms.

These differences suggest that mutations have consequences on RNA's transcription (transfer RNA, especially ribosomal) in particular, on myelination genes in patients with POLR3B mutation and on myelin retention and stabilization genes in POLR3A mutated patients.

CO 08

AVXS-101 PHASE 1 GENE-REPLACEMENT THERAPY (GRT) CLINICAL TRIAL IN SPINAL MUSCULAR ATROPHY TYPE 1 (SMA1): 24-MONTH EVENT-FREE SURVIVAL AND ACHIEVEMENT OF DEVELOPMENTAL MILESTONES

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Objectifs: SMA1 is a rapidly progressing, debilitating neurodegenerative disease caused by bi-allelic deletion/mutation of the survival motor neuron 1 (*SMN1*) gene, resulting in motor neuron loss, muscle weakness, respiratory failure, and early death. Children with SMA1 do not sit unassisted, almost none achieve a Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score ≥40 by 6 months, and 92% die/require permanent ventilatory support by 20 months. AVXS-101, a one-time investigational GRT, treats the genetic root cause of SMA, and is designed for immediate, sustained expression of SMN protein, allowing rapid onset and durable effect because it targets non-dividing neurons.

Contenu: In the phase 1 trial (NCT02122952), symptomatic SMA1 patients received a one-time intravenous dose of AVXS-101 at low (cohort 1, n=3) or proposed therapeutic dose (cohort 2, n=12). Primary objective was safety; secondary objectives were survival (avoidance of death/permanent ventilatory support) and sitting unassisted. CHOP-INTEND scores and other motor milestones were recorded. At 24 months, all patients were alive without need for permanent ventilatory support. Motor function improved in cohort 2 patients: 11/12 had CHOP-INTEND scores ≥40; 11/12 sat unassisted ≥5s, 10 for ≥10s, 9 for ≥30s; 11/12 had head control; 9 rolled over. Two patients crawled, pulled to a stand, stood, and walked independently. In the long-term follow-up study, 2 more patients sat unassisted ≥30s and 2 stood with support ; 3/4 received no medicinal treatments besides AVXS-101. No patient received nusinersen during the 24-month study period. Four patients had an asymptomatic transient rise in serum aminotransferase.

Conclusion: In contrast with natural history, AVXS-101 showed dramatic improvements in survival, motor function, and achievement of motor milestones of cohort 2 patients. No waning of effect or regression in motor function was reported.

CO 09

ACUTE FLACCID MYELITIS: AN EMERGING DISEASE WITH SEVERAL CHALLENGES. A RETROSPECTIVE STUDY OF AN ITALIAN COHORT

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Background and purpose: Acute Flaccid myelitis (AFM) is a polio-like illness defined by the acute onset of flaccid paralysis associated with longitudinal lesion in the gray matter of the cord on spinal MRI. A connection with EV-D68 infection have increased in recent years and the evidence for a causal link is growing but a definite etiology has yet to be established. There were clusters of AFM in US and Europe in 2014, in 2016 and in 2018. While most reports suggest some improvement, long-term outcomes are thought to be poor, although there are limited data on the natural history of this condition. The efficacy of intravenous immunoglobulin (IVIG) has not been systematically studied even though IVIG are the only treatment that has been found to have some efficacy in preventing progression to neuroinvasive disease. We describe clinical features, investigation findings and outcome (follow-up from 3 to 27months) of a series of five children with AFM (3 months - 12 years) observed in our Hospital (2016 and 2018).

Methods : this is a retrospective cohort study.**Results:** In three children initial symptoms were four limb weakness with hypotonia followed by flaccid paralysis. Two children presented with rigor and back pain without severe weakness. Febrile illness, with respiratory (3/5) or gastrointestinal (1/5) symptoms preceded (3-14 days) the onset of neurological symptoms. One child required intensive care support because of respiratory paralysis and myocarditis. Cerebrospinal fluid examination showed pleocytosis with raised cerebrospinal fluid protein in all, intrathecal synthesis of IgM was documented in 3/5. Spinal MRI documented typical findings in the acute phase and normalized during the follow-up; brainstem and cerebellar involvement was documented in 2/5 children. EV-D68 infection was not documented.

Four children showed complete clinical recovery at the last neurological assessment. One has persistent severe flaccid paraparesis.

Conclusions : AFM is a rare but severe disease, and we have much to learn about etiology, treatment options and clinical and diagnostic definition. Case identification is dependent on awareness among clinicians. Adequate viral diagnostics on respiratory samples and the capability of laboratories to type EVs are crucial in order to identify case related to EV-D68 infection.

CO 010

EPILEPSY AND EEG PATTERNS IN CHILDREN DIAGNOSED WITH HYPERINSULINISM. REPORT OF 2 CASES PRESENTED AS ATYPICAL GENERALIZED EPILEPSY AND REVIEW OF EEGS OF 15 SUPPLEMENTARY CASES

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Purpose: Hyperinsulinism is a rare genetic disorder with a heterogeneous presentation. Its severity ranges from severe, life-threatening hypoglycemia in newborns, to mildly symptomatic hypoglycemia beginning in childhood, adolescence or adulthood. Hypoglycemic loss of consciousness and seizures are the most common presentations. EEG patterns are not well known, and patients may be erroneously diagnosed with epilepsy. We tried to better characterize EEG datas in a cohort of patients with hyperinsulinism.

Methodology: Two cases of hyperinsulinism were diagnosed after an initial follow-up for epilepsy in our department. We then identified all patients followed for hyperinsulinism in the endocrinology department since 2000 and their respective EEGs were reviewed.

Results: The two index cases are those of an 8-month-old infant and a 14-year-old adolescent. Their EEGs were reviewed including an episode of hypoglycemia verified for each one of them (without epileptic seizure on the EEG). We found an inconstant slowing, focal or diffuse, with very slow notched waves or spikes or polyspikes, isolated or in bursts. During hypoglycemia we found an accentuation of these slow notched waves, with an EEG-tracing, with progressively increasing amplitude and delta frequencies. In the second patient a glucose infusion under EEG recording, resulted in an immediate disappearance of the pathological pattern. The interictal pattern in both patients was consistent with generalized yet atypical epilepsy. Another 15 hyperinsulinic patients were identified and twelve of them had an EEG. These EEGs were normal in 6 patients. Five patients had focal abnormalities, and one patient had a temporo occipital slowing.

Conclusion: Our two patients had no revelation of their hyperinsulinism by clinical suspicion of hypoglycemia but presented themselves as having epilepsy. Interestingly although their initial EEG-tracings revealed epileptic abnormalities, these were different from those seen during their proven hypoglycemic episodes. This could lead to the hypothesis of an altered cerebral activity with further epileptogenesis resulting from untreated repeated hypoglycemia.

CO 011

PROPOSAL OF A NEW DIAGNOSTIC SCORE FOR AICARDI-GOUTIÈRES SYNDROME

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OBJECTIVES: Aicardi-Goutières Syndrome (AGS) is a rare inherited neurological condition related to an abnormal up-regulation of type I interferon signalling. To date, mutations in 7 genes have been associated with AGS. Clinical diagnostic criteria have been established when the syndrome has been described. With the discovering of the genetic causes of the disease and due to recent use of next generation sequencing (NGS) techniques, we assisted to the progressive widening of the clinical spectrum of AGS-related phenotypes including atypical cases and "non-AGS presentation". In fact, some already knew conditions such as Retinal Vasculopathy with Cerebral Leukodystrophy (RVCL) and Singleton Merten Syndrome, has been found to be caused by AGS-genes, as also previously unknown phenotypes like bilateral striatal degeneration, spastic paraparesis, and other still unclassified clinical pictures. Even if current AGS diagnostic criteria appear helpful to recognize classic AGS, they are not able to discriminate atypical and non-AGS phenotypes.

METHODS: We revised AGS diagnostic criteria according to recent advances in the field, in order to produce an expert-based and up to date diagnostic score.

We retrospectively selected a group of patients with a clinical diagnosis of AGS and/or harbouring pathogenic mutations in one of the seven AGS-genes. Each patient was classified as affected by classic AGS, atypical AGS and "non-AGS" on the basis of clinician experience on the disease. On the same series of patient, we applied our proposed diagnostic score.

RESULTS: A total of 20 patients have been selected. 12 patients received a score consistent with classic AGS, 5 with atypical AGS and 3 with "non-AGS". The score results coincided with the "gestaltic" diagnosis on 100% of cases.

CONCLUSION: Based on our experience on the disease and based on literature available data we propose an update of the diagnostic criteria for AGS. Our score represents a standardized tool able to distinguish classic and atypical AGS and this will be useful for new studies on the disease. The three groups should be compared in order to find out if there are any genetic and non-genetic factors that have influenced the final phenotype. Moreover, this classification will be helpful in designing forthcoming clinical trials. Larger series of patients will be needed in order to validate our scoring system.

CO 012

EVALUATING THE PERFORMANCE OF METAGLUT1 IN PATIENTS WHOSE CLINICAL PRESENTATION IS COMPATIBLE WITH THE GLUCOSE TRANSPORTER 1 DEFICIENCY SYNDROME (GLUT1 DS)

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Objectifs : The diagnosis of Glut1 DS can be challenging due to the phenotypic heterogeneity among patients, coupled to confirmation that relies on the one hand on a measure of cerebral spinal fluid (CSF) glucose concentration typically reduced, but not always, and requires an invasive procedure. On the other hand, genetic analysis of the SLC2A1 gene can lead to results which are difficult to interpret.

The METAglut1 blood test was able to detect a significantly lower expression of GLUT1 at the surface of red blood cells among 23 out of 30 patients tested who had been diagnosed with the disease. The current study will allow a large-scale evaluation of the test's performance and has received a grant through the Forfait Innovation scheme from the French Ministry of Health and the High Authority for Health (Haute Autorité de Santé, France).

Contenu: When a patient presents clinical symptoms suggesting a GLUT1 deficiency, a METAglut1 test will be systematically performed blindly from the reference strategy consisting in the measure of CSF glucose concentration complemented genetic analysis. The study is multicentric and patients, children and adults, will be recruited in more than 40 centers all over France. The main goal will be to estimate the concordance between the METAglut1 test and CSF glucose concentration among all patients with a diagnostic of certainty (either positive or negative) in the prospective cohort. Patients already diagnosed can be included in a retrospective arm to strengthen exploratory the data. A medical and economic analysis will be performed to evaluate the patients' care pathway.

Conclusion: This study will allow to evaluate the diagnostic benefit of the METAglut1 test and its place in the diagnostic strategy of the GLUT1 deficiency syndrome. The confirmation of the high performance of the test will be very valuable as it only requires a simple venous blood test, no need for fasting, and is characterized by a quick turnaround time, to improve the early detection of patients which is of prime importance in this neurological pathology for which efficient therapies are available.

CO 013

NEW STRATEGIES TO ASSESS NEUROPSYCHIATRIC INVOLVEMENT AND IMPROVE THE OUTCOME IN CHILDREN AND ADOLESCENTS WITH NF1 AND TSC

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OBJECTIVES: The prevalence of neuropsychiatric problems in Neurofibromatosis type 1 (NF1) and Tuberous Sclerosis Complex (TSC) is relevantly higher than in the general population. In TSC has been developed a TAND (Tuberous Sclerosis Associated Neuropsychiatric Disorders) Checklist to quickly assess those symptoms. Aim of the study is testing the overall usability of the TAND Checklist in NF1 and comparing the cognitive/behavioral profile in NF1 and TSC in our clinical cohorts of patients.

METHODS: 84 patients, aged 4 to 20 years old, were screened with the Italian version of the TAND Checklist: 42 with TSC (23 F and 19 M, mean age 11,36 +/- 4,2 years) and 42 with NF1 (23 F and 19 M, mean age 11.33 +/- 4,2 years). We collected the clinical informations from disease specific follow-ups and neuropsychiatric comorbidities previously diagnosed according to DSM-V. Cognitive level was assessed through standardized scales.**RESULTS:** TAND-Checklist NF1 cohort : 9,5% had ID (Intellectual Disability), 21,4% SLD (Specific Learning Disorders), 16,7% ADHD (Attention Deficit Hyperactivity Disorder) and 11,9% anxious/mood disorder. No one had diagnosis of ASD (Autistic Spectrum Disorder). The problems highly reported were: paying attention and concentrating (59,5%), impulsivity (52,4%), anxiety (50%), overactivity/ hyperactivity (38,1%), temper tantrums (38,1%), academic difficulties (> 40%), deficits in attention (59,5%) and executive skills (38,1%).

TAND-Checklist TSC cohort: 35.7% had ID, 12% SLD, 14,3% ADHD and 4,8% anxious/mood disorder. 9,5% had formal diagnosis of ASD. The problems highly reported were: paying attention and concentrating (61,9%), impulsivity (54,8%), temper tantrums (54,8%), anxiety (45,2%), overactivity/hyperactivity (40,5%), aggressive outburst (40,5%), absent or delayed onset of language (40,5%) and repetitive behaviours (35,7%), academic difficulties (> 40%), deficits in attention (61,9%) and executive skills (50%).

Neuropsychiatric features NF1 VS TSC: There was statistically significant higher reports in TSC than in NF1 for aggressive outburst and self-injury and ASD features.

CONCLUSIONS: TAND Checklist was acceptable and feasible to complete in a clinic setting and was able to detect the complexity of neuropsychiatric involvement in NF1. According to previous findings NF1 is mainly characterized by ADHD profile, anxiety problems and SLD. Comparing the two conditions ASD features were strongly associated to TSC; in NF1 those features were reported in less than 15% of the patients. TAND-Checklist is a useful and reliable screening tool, both in TSC and NF1.

CO 014

AN AUTOMATED EEG GRADING SYSTEM FOR THE EARLY NEONATAL BRAIN INJURY SEVERITY PREDICTION POST-PERINATAL ASPHYXIA

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Objectifs: To develop a quantitative EEG-based automatic grading system for neonatal hypoxic-ischemic encephalopathy (HIE).

Methods: Neonatal EEG were recorded in full term infants in the first 6 hours of life after perinatal hypoxia. The severity of HIE was determined by the visual conventional EEG grades (French classification), assessed by two neurophysiologists blinded to clinical data. Six EEG quantitative features were selected based on their correlation scores with the 3 visual grades. Thereafter, the 6 selected features were analyzed using Discriminant Factorial Analysis (DFA) to predict the severity grade and the long-term outcome.

Results: 90 EEG were analyzed between 2013 and 2017. The EEG quantitative features measuring the discontinuity and the amplitude of the signal were able to discriminate the 3 visual grades. The DFA results showed an accuracy of 86.7% for predicting EEG grades and 79.8% for predicting outcome at one year.

Conclusion: The proposed automated system using DFA was effective for grading initial EEG and predicting long-term outcome early after perinatal asphyxia. This system is based on simple quantitative features already proposed in marketed programs and could be easily used in clinical routine by unexperienced users. It may facilitate the evaluation of HIE's severity within 6 hours after birth and then be useful to determine whether therapeutic hypothermia has to be initiated.

CO 015

EARLY DIAGNOSIS AND SPEED TO EFFECT IN SPINAL MUSCULAR ATROPHY TYPE 1 (SMA1)

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Objectifs: SMA1 is a rapidly progressing disease resulting in death or need for permanent ventilation by 2 years of age ; early intervention with disease modifying treatment is critical. In the pivotal phase 3 nusinersen study (ENDEAR; NCT02193074), ~10% of patients died/required permanent ventilation within 2 months after initiation of therapy (time required for 4 loading doses); 39% of patients died/required permanent ventilation by 6 months from dosing. This may reflect a non-immediate therapeutic impact related to the loading dose schedule. This study explored rapidity of therapeutic effect of onasemnogene abeparvovec (AVXS-101) gene-replacement therapy (CL-101 phase 1 study; NCT02122952), as measured by early changes in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score, compared with the response to nusinersen in ENDEAR (≤5-point increase at 2 months post-dosing).

Contenu: Symptomatic SMA1 infants were treated with a one-time AVXS-101 intravenous injection (cohort 2 ; N=12; 24 months follow up). Outcomes of interest were event-free survival (EFS; CL-101: death or ≥16 hours ventilation/day for >2 weeks; ENDEAR: death, tracheostomy, or ≥16 hours ventilation/day for >21 days) and motor function improvements from baseline using CHOP-INTEND. All 12 AVXS-101–treated patients showed EFS at study end, versus 49/80 (61%) nusinersen patients. At 1, 3 and ~10 months post–AVXS-101 treatment, CHOP-INTEND increased 9.8, 15.4, and 27 points, respectively. At 2 and ~10 months post-nusinersen initiation, CHOP-INTEND increased ≤5 and ~10 points, respectively. By 6 months, 11/12 (92%) AVXS-101–treated patients achieved CHOP-INTEND scores ≥40 versus 30/78 (38.5%) nusinersen-treated patients at last interim data-cut (day 183–394).

Conclusion: AVXS-101 appears to improve survival and induce more rapid motor function improvements compared with nusinersen. Advances in understanding SMA underscore the need for early diagnosis and treatments with a near-immediate onset of action to maximize clinical improvements.

CO 016

EARLY-ONSET EPILEPTIC ENCEPHALOPATHY RELATED TO GERMLINE PIGA MUTATIONS: A SERIES OF FOUR PATIENTS

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Objectifs: Phosphatidyl inositol glycan class A (PIGA) is involved in the synthesis of glycosylphosphatidylinositol (GPI). PIGA protein is present in many organs, including brain, kidney, liver, erythrocytes. *PIGA* gene is located on X–chromosome (Xp22.2). Its size is 162 kB. Somatic mutations in *PIGA* create paroxysmal nocturnal hemoglobinuria (PNH) while germline mutations are linked to epileptic encephalopathies, with a wide range of phenotypes including numerous severe forms.

Contenu: We report a series of four patients exhibiting germline mutations in the *PIGA* gene. All patients were boys. They were all born with normal birth parameters. They exhibited early epileptic encephalopathy, with infantile spasms or partial seizures beginning between 4 months and 1 year of age. Only one child (patient#4) exhibited mild dysmorphic signs. No pattern of suppression burst was present on EEG, but atypical hysparrythmia was noted in patient #2, and patient #1 exhibited multifocal slow spike-waves that were initially suggestive of migrant epilepsy. No typical MRI features were noted at first evaluation, with one boy exhibiting a thin corpus callosum. One patient experienced a progressive cerebellar atrophy. White matter abnormalities and cerebral atrophy were present in all patients during follow-up. Alkaline Phosphatases were elevated in two patients. Patients #1 and #2 exhibited renal cysts. Half of the patients were bearing a mutation inherited from their asymptomatic mothers. A ketogenic diet was tried in three cases, but to no effect. All cases exhibited severe mental retardation, with developmental delay and severe epilepsy. Patients #1 and #3 died respectively at age 8 and 14.

Conclusion: Germline *PIGA* mutations are a X-linked disorder leading to severe encephalopathy. To date a few cases are reported (Johnston 2012, Van der Crabben 2014, Belet 2014, Swoboda 2014, Kato 2014, Lin 2018). The dysmorphic signs reported until now may be absent, and MRI is poorly informative. Epilepsy is severe with no specific treatment to date. However, renal cysts and elevated Alkaline Phosphatases are important clues that should prompt *PIGA* sequencing in a boy experiencing early encephalopathy.

CO 017

BIALLELIC PDE2A MUTATIONS: A NEW CAUSE OF INTELLECTUAL DISABILITY WITH PAROXYSMAL DYSKINESIA AND/OR EPILEPSY

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Background: Several genetic causes of paroxysmal dyskinesia have been revealed during the last years. However, the cause of complex dyskinesia remains elusive in some patients. A homozygous loss-of-function mutation in the 3',5'-cyclic nucleotide phosphodiesterase PDE2A gene was recently reported in one patient with childhood-onset choreodystonia. The choreodystonia was preceded by paroxysmal dyskinesia and associated with cognitive impairment and interictal EEG abnomalities. Here, we report on three new cases (two children sibs and one adult) with biallelic PDE2A mutations to delineate the phenotype related to this gene.

Methods: The patients' DNA underwent trio whole-exome sequencing. A retrospective analysis of their phenotype with video-documented movement disorder is reported.

Results: We identified in PDE2A a homozygous gain of stop codon mutation (c.1180C>T; p.(Gln394*) in the siblings and compound heterozygous mutations in the young adult patient (missense c.419C>T; p.(P140L) and splice-site mutation). All three patients had a cognitive impairment or developmental delay. The phenotype of the two oldest patients, aged 9 and 28 years-old, was characterized by childhood-onset refractory paroxysmal dyskinesia initially misdiagnosed as epilepsy due to interictal EEG abnormalities. One of them developed chronic choreodystonia in the disease course. The youngest patient aged 15 months showed a documented epilepsy at the age of 4 months and no paroxysmal dyskinesia to date.

Conclusions: Together with the previously reported case, our three patients confirm that biallelic PDE2A mutations are a cause of childhood-onset refractory paroxysmal dyskinesia with cognitive impairment, sometimes associated with interictal baseline choreodystonia and EEG abnormalities or epilepsy.

CO 018

PRIMARY AND SECONDARY STEREOTYPIES IN CHILDREN: A PILOT STANDARDIZED PROTOCOL AND VIDEO ANALYSIS

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Objectifs: There is still a great interest in repetitive and stereotyped behaviours (RSB) and self-injurious behaviours (SIB) in children, either in typically developing children, because of their evolution in time and children's developmental profile, either in neurodevelopmental disorders, since they cause functional impairment in daily life. Our study aims to further characterize these behaviours using a standardized protocol and videotaped play-session.

Contenu: Twenty children with primary stereotypies (PS, n=20) and 63 children with secondary stereotypies (SS) diagnosed with autism spectrum disorder, (ASD, n=22) developmental delay/intellectual disability (DD; n=21) and blindness (VI; n=20), aged from 2 to 12 years old, were assessed. Characteristics of RSB (**family history, age of onset, frequency, duration, complexity, triggers, clinical features**) were collected by medical history. Repetitive behavior scale-Revised (RBS-R) and Child Behavior Checklist (CBCL) were completed by the children's caregivers. Frequency, duration and types of stereotypies were coded from 20 minutes of a videotaped standardized play-session. Mean age at evaluation was 53.0 months for ASD (DS 14.7, range 30-96), 78.9 months for VI (DS 31.2, range 24-132), 70.8 months for DD (DS 32.4, range 24-144), 74.2 months for PS (DS 28.3, range 24-144). Family history of stereotypies was identified in 30% of PS sample. Mean age of onset was before 24 months in 100% of our sample. Symptoms usually occurred more than once a day, but SIB and RBS were reported at higher scores on the RBS-R in Secondary group. Stereotypies lasted less than 5 minutes in ASD, DD and PS groups, and from 5 minutes to 1 hour in the VI sample. PS group showed more complex motor stereotypies than secondary groups, which presented more motor and phonic ones. Excitement was identified as a trigger in more than 80% in every group. Flapping and complex upper limbs movements were the most frequent repetitive behaviours in PS, otherwise self-directed movements (gaze hands, covering ears) were common features in secondary stereotypies. Children with ASD had the highest frequencies of gait stereotypies, while self-injurious behaviours were frequent in VI and DD groups.

Conclusion: Few studies have compared primary and secondary stereotypies including a visual impairment group. Despite similarities, differences in RSB and SIB are evident in primary and secondary stereotypies. PS show more complex movements, but the secondary group have more motor and phonic stereotypies. Self-directed stereotypies tend to be common feature of SS, while SIB seem to be related to low IQ and/or sensory impairment.

CO 019

THE TREATMENT BY SMALL DOSE OF VALPROIC ACID FOR AUDITORY HYPERSENSITIVITY IN AUTISM SPECTRUM DISORDER

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Introduction: The children of autism spectrum disorder (ASD) suffer from various complications. Auditory hypersensitivity (AH) is one of them. The mechanism is not clear and effective treatments are not found. Some reports suggest that AH is caused by decreased inhibitory processing resulting from abnormal sensory gating system or dysfunction of inhibitory interneurons, and the abnormalities in the GABAergic interneurons and/or in the serotonin/dopamine system. We report here our experience to treat AH in ASD children by a small dose of valproic acid (VPA).

Materials and Methods: The materials were 7 children (2 males; M1-2 and 5 females;F1-5) of ASD with severe AH from the age of 5 to 11 years. They were suffered from noises of vacuum cleaner, noises at platform, echo in a pool, siren of ambulance etc. Six cases took Yokukansan (Japanese herbal medicine with serotonergic functions) at first as emotional stabilizer but not effective for AH. F2 took VPA as the initial treatment for AH. VPA was used with the dose of 5.1 to 8.3 mg/kg/day.

Results: In all cases, AH phenomena became milder (F3,4,5) or disappeared (F1,2, M1,2). F1 who suffered from various noises, especially sound to wash out in a lavatory became free from earmuffs, the monthly panic in F2 triggered by a chime of microwave oven, sound of boiled water etc. disappeared within a month.

Conclusions: The treatment by small dose of VPA for AH in ASD showed successful effects, This treatment has a value to be tried.

CO 020

EPILEPSY IN INV DUP (15) SYNDROME: CLNICAL AND ELECTROPHYSIOLOGICAL FEATURES IN A CASE SERIES OF FOUR PATIENTS

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Objectives and background: This study aims to review and contribute to electro-clinical features of inverted duplication of proximal chromosome 15 (inv dup (15)) syndrome. Inv dup (15) syndrome results from the instability of chromosome region 15q11-q13 and is most frequently associated with autism spectrum disorders. Affected patients also typically present with developmental delay and intellectual disability, hypotonia, expressive and comprehensive language disorders, movement disorders and epilepsy. All of these patients carry a supernumerary chromosome 15 marker resulting in tetrasomy 15q, a region that involves the critical for neurodevelopment genes: UBE3A and SNRPN. Although epilepsy is recognized as a major challenge in the management of inv dup (15) syndrome, electro-clinical data are limited and heterogenic.

Methods: A 5- year retrospective review of clinical notes, electronic patient records and (video) electroencephalographic recordings of patients followed in our Department for epilepsy associated with inv dup (15) syndrome.

Results: Medical records of four patients were reviewed. Several ictal and inter-ictal EEG recordings and long-term follow-up were available for all patients. The majority of recorded seizures were classified as generalized tonic seizures, often occurring in clusters. Other rare types of recorded seizures include clusters of spasms (characteristic tonic seizure a minima or tonic spasm pattern), atonic and generalized tonicoclonic seizures. Electrophysiological findings consist of multiform abnormalities on a disorganized background activity. Extended diffuse beta rhythm activity is found in all patients' EEG recordings and seems more prominent during epileptic manifestations.

Conclusion: We recognize in this case series a significant predominance of tonic seizures of variable duration. Although generalized tonic seizures have been described in patients with inv dup (15), previous reports refer to spasms as the most frequent type of seizures. The excess in beta rhythm activity is highlighted among other EEG abnormalities and could correspond to an electrophysiological bio-marker, supporting the relevant theory of Frohlich et al. An electro-clinical pattern of generalized epilepsy with tonic seizures and predominant diffuse fast rhythms is thus outlined in these four patients with inv dup (15) syndrome. Prospective studies are needed in order to confirm reported electro-clinical data and to establish genetic/ prognostic correlations.

CO 021

CHARACTERISTICS OF POLYHANDICAPPED PATIENTS. ABOUT A 875 PATIENTS COHORT

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Objectifs: Polyhandicap (PLH) is a complex disability condition corresponding to a chronic affliction occurring in an immature brain, leading to a combination of a profound mental retardation and a serious motor deficit, resulting in an extreme restriction of autonomy and communication. These patients are completely dependent on human and technical assistance. To improve the knowledge concerning this population of patients we implemented a cohort study, the aim of this cohort was to describe the characteristics of patients with severe PLH.

METHODS : Patients were included from 4 specialized reeducation centers, one residential facility and home, PLH defined by the combination of motor deficiency, profound mental retardation, intelligence quotient <40, Functional Independency Measure <55), Gross Motor Function Scale III, IV, V, age at onset of cerebral lesion below 3 years old. **Data collection:** socio demographic data, etiology, biological and clinical data, associated handicaps (epilepsy, sensorial deficiency, chronical pain, swallowing disorders, behavior disorders, medical devices…), developmental state (posture, language, sociability, communication), main vital functions (orthopedic, digestive, urinary, respiratory, neurology).

RESULTS: A total of 875 PLH patients were included in the cohort. Mean ages 24.6+/-16.8 (3-68), 45.8% children, 54.2% adults, 53.3% male, 46.7% female, etiology of PLH was unknown in 15.2% of cases,76% were congenital, 24% were acquired. Comorbidities of PLH patients: 26.3% hip luxation, 57.2% scoliosis, 15% had arthrodesis, 70.5% limb deformations 35.8% had swallowing disorders, 31.6% had a gastrostomy, 40.5% gastro esophageal reflux, 55% epilepsy and 26.% presented previous status epilepticus, 10.5% presented one or more than a seizure/day, 28.6% visual impairment, 5% hearing impairment, 72.2% behavior disorders, 91% were incontinent, 92% do not have any articulated language, 20.5% had chronicle bronchial congestion. General developmental level according of the 4 domains of Brunet-Lézine scale were: for posture domain: 5.5+/-4.5 months, coordination domain 5+/-4.4 months, for language domain 5.5+/-5.1 months, for socialization domain 6+/-5.4 months.

Conclusion: Polyhandicap is a dramatic condition consequence of various etiologies mostly of congenital origin, most of these patients present associated handicaps and severe comorbidities mostly orthopedic, digestive and respiratory, their mean developmental level is below7 months. This is to our knowledge, the first important survey describing clinical characteristics of severe polyhandicapped patients.

CO 022

A NOVEL HYPOMYELINATING LEUKODYSTROPHY CAUSED BY LOSS OF THE SPHINGOLIPID DESATURASE DEGS1 WITH POTENTIAL THERAPY

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Objectifs: Leukodystrophies (LD) are a heterogeneous group of neurogenetic disorders that primarily affect the brain's white matter. Despite progress in clinico-MRI classification and genomics, many cases remain unexplained with an unknown biochemical or molecular basis. Our objective was to identify genes involved in the ultrarare forms of undetermined leukodystrophies

Contenu: We have used whole exome sequencing in 80 families with undetermined leukoencephalopathies, collected in the LEUKOFRANCE network. In 3 families, we found mutations in the endoplasmic reticulum lipid desaturase DEGS1 gene. Clinical presentation among the 4 affected patients included absence of motor acquisitions with dystonia and nystagmus, severe spasticity, profound failure to thrive in 2 cases, and early onset progressive spasticity in 2 cases. MRI showed hypomyelination in the deep white matter with thinning of the corpus callosum, and progressive thalami and cerebellar atrophy in the most severe cases associated in one case with a.demyelinating neuropathy. Due to the large clinical severity found among the 3 families, we asked for additional DEGS1 mutated patients through our European network for leukodystrophies and the GeneMatcher platforms. Fifteen additional patients from 10 unrelated families were identified. DEGS1 converts dihydroceramide (DhCer) into ceramide (Cer) in the final step of the de novo biosynthesis pathway. A marked increase of the substrate DhCer and DhCer/ Cer ratios in patient's fibroblasts and muscle was demonstrated.

Finally, a knockdown approach for disease modelling in Danio rerio, followed by a preclinical test with fingolimod (FTY720, Gilenyaâ) demonstrated the potential therapeutic interest of this molecule reducing the critical DhCer/Cer imbalance and the severe locomotor disability.

Conclusion: This new group of neurodegenerative disorders confirm the deleterious effect of sphingolipid imbalance, alreading involved in demyelinating leukodystrophies, such as Krabbe disease and metachromatic leukodystrophy, among others.. In addition, this study highlights the interest of using freely accessible information exchange platforms such as GeneMatcher after exome sequencing, for rapid identification of sufficient cases to delineate a disease spectrum and improve management

CO 023

CONGENITAL IMMOBILITY AND STIFFNESS DUE TO ATAD1 BIALLELIC MUTATIONS. REPORT OF TWO NOVEL UNRELATED PATIENTS

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Objectifs: To describe the congenital encephalopathy related to the *ATAD1* gene.

Contenu: The ATAD1 gene encodes for thorase, a protein that regulates the expression of postsynaptic excitatory glutamatergic AMPA receptors. Six patients from three families with biallelic mutations in ATAD1 have been reported to date. All had a congenital encephalopathy characterized by global hypertonia, poor or absent motility, feeding and breathing difficulties, poor eye contact and limited responsiveness to stimuli. Four of them died in the first moths of life. We report on two novel patients with this congenital immobility and stiffness ATAD1-related (CISAR) syndrome. Patient #1 needed intensive cares from birth because of severe stiffness with axial hypotonia, immobility with inexpressive facies, limited responsiveness to stimuli, inability to feed up and tenuous breathing. He had epileptic seizures at 5 months and died at 6 months. Whole-exome sequencing (WES) revealed the novel homozygous p. (Gly128Val) variant in ATAD1. Patient #2 had a similar disease course, except that he had no epilepsy. He died at 4 months of cardio-respiratory failure. We found by WES the previously reported p. (His357Argfs*15) ATAD1 homozygous variant in this patient's DNA. Both patients had null auditory evoked potentials.

Conclusion: The phenotype of both patients was close to that of published patients, extremely severe from birth (see videos) to their early demise. We confirm absent auditory evoked responses in CISAR, which is likely related to the role of AMPA receptor in auditory signals processing. The diagnosis of CISAR should be taken into consideration in new-borns with extreme stiffness, along with BRAT1-related encephalopathy.

CO 024

RESIDUAL VERY LOW DYSTROPHIN LEVELS MITIGATE DYSTROPHINOPATHY TOWARDS BECKER MUSCULAR DYSTROPHY

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Novel therapy approaches for Duchenne Muscular Dystrophy aim at restoring dystrophin expression. However, the minimal dystrophin restoration levels required to achieve clinical benefit remains unknown. Residual dystrophin expression can be observed in certain patients carrying DMD intronic (including splice sites) and nonsense mutations in exons for which deletion leads to in-frame transcripts. To determine whether expression of very low dystrophin levels can mitigate disease severity, residual dystrophin expression was correlated with disease severity of patients with these DMD mutations. Eighty patients were identified using the UMD-DMD-France database. Clinical data were obtained from medical care centres. Residual dystrophin expression was semi-quantitatively determined on Western Blots. Time-to-event analysis was performed for age of loss- of-ambulation as well as for respiratory, cardiac and orthopaedic endpoints and life expectancy. Patients with <5% dystrophin expression ambulated longer (n=33; median 45.6 years) than patients without dystrophin (n=47; median 10.3 years), ($p<0.0001$). Furthermore, patients with <5% dystrophin had longer survival ($p=0.0006$), delayed decline in vital capacity<20% ($p=0.0088$), later start of non-invasive ventilation ($p=0.0006$), tracheotomy ($p=0.0040$) and arthrodesis ($p<0.0001$). Conversely, residual dystrophin did not influence the age of occurrence of LVEF<30% ($p=0.2172$). Analysis of same endpoints for patients expressing <1% dystrophin (n=24) showed a similar shift towards slower disease progression. In conclusion, very low residual dystrophin expression is sufficient to shift the natural history of dystrophinopathy towards the milder Becker phenotype. These data suggest that restoration of low dystrophin levels might be sufficient to achieve long-term clinical benefit from novel therapeutic strategies. Results will be discussed in the light of the limited number of study subjects, time of observation and employed Western Blot methodology. The study is in progress and inclusion of more patients and time points of clinical follow-up will strengthen further accuracy of results.

CAS CLINIQUES

DDC1

A FORCED ROTATION OF THE HEAD IS NOT ALWAYS EPILEPTIC IN NATURE

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Objectifs: Paroxysmal events, characterized by a version of the head neck and with breathing movement's cessation, rapidly followed by an alteration or even a loss of conscious of a rather short duration, can be misdiagnosed, due to their stereotyped and repetitive character, as focal epileptic seizures. Brief tremors of the arms and head can also be observed. A concomitant diffuse slowing of the background activity can be seen on EEG. Paroxysmal events, characterized by a version of the head neck and with breathing movement's cessation, rapidly followed by an alteration or even a loss of conscious of a rather short duration, can be misdiagnosed, due to their stereotyped and repetitive character, as focal epileptic seizures. Brief tremors of the arms and head can also be observed. A concomitant diffuse slowing of the background activity can be seen on EEG.

Contenu: We report the electro-clinical characteristics in 3 children, including one with persistence of the manifestations in adulthood, who presented with stereotyped motor manifestations of neck rotation with impaired awareness, misdiagnosed as focal epilepsies. The paroxysmal events were in fact auto induced syncops, suggesting a "stretch syncope", an entity rarely reported. The underlying physiopathological mechanism is poorly understood. The most likely hypothesis would be related to changes in cerebro-basilar vascular flow. Differential diagnosis with episodes compulsively induced by Valsalva's manoeuvre will also be discussed.

Conclusion: Misdiagnosis of this syndrome leads to inappropriate overtreatment with antiepileptic drugs.

DDC2

DEVELOPMENTAL REGRESSION AND MYOCLONIC JERKS IN A TEN-MONTH-OLD BABY

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Background: Subacute Sclerosing Panecephalitis (SSPE) is a persistent and chronic encephalitis, which is an extremely severe complication of measles infection. Incidence of SSPE has dropped significantly since the introduction of mass campaigns for measles vaccination in most countries. Since 2017, a new outbreak of measles in Italy has been observed, which can be related to a non-adherence to the vaccination campaign.

Clinical case: The patient, a ten-month-old baby, contracted congenital Cytomegalovirus infection and measles infection from the non-vaccinated mother at the age of 6 weeks. She was not administered antiviral therapy. At the age of 10 months she presented sudden head and upper limbs movements, associated with a progressive developmental regression. Neurological examination revealed hypotonia, poor spontaneous movements, no head nor trunk control, no vocalization, irritability, absence of visual fixation, pyramidal signs. EEG showed periodic complexes and epileptic and non-epileptic myoclonic jerks. Serological investigation documented high titers of anti-measles IgG, anti-measles IgM were negative. Measles DNA was neither detected in blood. High titers of anti-measles IgG in CSF confirmed the diagnosis of SSPE. Oral antiviral therapy with inosine acedoben dimepranol and oral levetiracetam in order to control myoclonus were started. Interferon IFN-α was refused by parents. After four months, the patient showed progressive cognitive and motor deterioration, difficulty in swallowing, increase in number of periodic myoclonic jerks (>1/minute). At the age of 20 months, she is still alive; neurological examination shows severe hypotonia with dystonic movements, rare myoclonic jerks and absence of seizures; EEG periodic complexes disappeared, and delta slow wave activity is preminent.

Discussion: SSPE in the first year of life is described in very few cases. Our patient experienced a sudden clinical course without the well-defined stages of the typical form of SSPE, similar to the cases described in the literature that are characterized by a shorter latency and a rapid disease progression. We nevertheless urge the community about the risks of a non-adherence to the vaccination campaign, which is becoming recently increasingly common, with 5.407 cases registered by the Italian Health Care System in 2017. SSPE is a potentially lethal disease and eradication of measles infection by effective vaccination program is considered the most beneficial form of control.

DDC3

RASA1 MUTATION IN A CHILD WITH CAPILLARY MALFORMATION–ARTERIOVENOUS MALFORMATION SYNDROME / NOONAN-LIKE SYNDROME

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Objectifs: Capillary malformations (CMs) are the most common vascular anomaly of the skin. They consist of many dilated capillary-like channels in the dermis. Capillary malformation-arteriovenous malformation syndrome (CM-AVM) (OMIM #608354) is a recently recognized autosomal dominant inherited disorder that occurs in 1:100,000 individuals. CM–AVM is characterized by multiple small CMs associated with either AVMs or arteriovenous fistulae (AFVs,) fast-flow vascular anomalies. CM-AVM is caused by mutations in RASA1 (MIM #139150) which encodes the Ras p21 protein activator 1, which helps to regulate RAS/MAK, (Mitogen-Activated-Kinasas).

Noonan syndrome (NS) is a common autosomal dominant developmental RASopathy. Genes of the Ras/mitogen-activated protein kinase pathway including: PTPN11, SOS1, RIT1, KRAS, NRAS, RAF1, SHOC2, SOS2, LZTR1 and CBL. The mutations involved in NS are considered a gain of function mutation.

NS is characterized by distinctive facial dysmorphism, short stature, congenital heart defects and other heterogeneous, phenotypic manifestations. Features include hypertelorism, low-set ears, blue irises, ptosis, mild neck webbing, high forehead, down-slanting palpebral fissures, and epicanthic folds. NS is considered present if the patient has this typical facial dysmorphology plus one of the typical diagnostic criteria findings (or two minor criteria).

Contenu : The patient is a 5-year-old female who was presented to the neurology clinic for the first time at 1 year of age. She is the first daughter of a young, healthy, non-consanguineous couple. Her family history was negative for neurologic hereditary disease. At 4 years of age she underwent a spinal cord and brain angio-MRI. The results showed no central nervous system pathology. The examination includes short stature, pectus excavatum, bilateral ptosis, two café-au-lait spots, and multiple small CMs throughout the body.Complete analysis was normal, including celiac disease and thyroid hormones. Ophthalmological exam, Cardiovascular examination and abdominal ultrasound were normal. Parents were concerned about symptoms of attention deficit and slow learning. The tests of intelligence showed a limit IQ due, above all, to a decrease in working memory. Based on the diagnostic criteria of NS, the patient fulfilled enough criteria to confirm it. Genetic testing identified a heterozygous RASA1 gene variant (c.1253 + 2T> G). Sanger test of parents was normal.

Conclusion: To our knowledge, this is the first case of CM-AVM associated with NS. Since NS is a RASopahty, this phenotype is probably underdiagnosed in patients with mutations in RASA1/CM-AVM.

P01

PREDICTIVE FACTORS AND PROGNOSTIC VALUE FOR STATUS EPILEPTICUS IN NEWBORNS

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Objectifs: To evaluate the predictive factors for status epilepticus (SE) in neonates and prognostic factors for patient outcomes in newborns suffering from seizures.

Methods: A retrospective single-center study from January 2010 to December 2014, included 91 newborns who had neonatal seizures, among them, 50 newborns presented SE and 41 newborns presented isolated seizures. SE was defined as a single seizure lasting more than 15 min or repeated seizures without return to preictal neurological baseline for more than 15 min. Isolated seizures were defined as one single seizure lasting less than 15 minutes or more seizures with complete recovery of consciousness between seizures. Perinatal and electroclinical data were recorded. Outcomes were evaluated at one year follow up. Results: In multivariate analysis, the factors identified as being predictive of SE were a severely abnormal initial neurological examination (OR 15.7, 95% CI (3.8–109) p=0.00075) and hypoglycemia (OR 6.8, 95% CI (1.5–49.2) p=0.024), found mostly in newborns with hypoxic-ischemic encephalopathy. SE was found to be a negative prognostic factor for outcome only in univariate analysis. The only independent prognostic factor found was the posticta clinical examination, normal results being associated with a more favorable evolution (OR 73.918, 95% CI (13.700-715) p <0.0001).

Conclusion: Two independent risk factors for SE in newborns have been identified : a severely abnormal initial neurological examination and hypoglycemia. The only positive prognostic factor was found to be a normal posticta clinical examination.

P02

LONG TERM NEUROCOGNITIVE IMPROVEMENT AFTER RIGHT HEMISPERECTOMY PERFORMED AT THE AGE OF FIVE: CASE REPORT AND REVIEW OF THE LITERATURE

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Objectifs: We present the long-term neurocognitive changes of a right-handed girl with intractable epilepsy after late right hemispherectomy.The girl was affected by an epileptic encephalopathy associated with right frontotemporoparietal polymicrogyria; she was submitted to neurosurgery at the age of 5 and examined with last neuropsychological tests at the age of 17 years. She took advantage of neurocognitive rehabilitation for several years. She is currently seizure-free and off therapy.

Contenu: Early childhood hemispherectomy, prior to puberty, can benefit satisfactory cognitive development thanks to brain plasticity. The comparison of tests performed in children with mixed pathology before and after surgery shows a cognitive improvement with a developmental IQ increase of more tha 15 points. Regardless of the surgery side there is a significant discrepacy between verbal IQ, which is significantly higher than performance IQ. Sixty-one percent of children have no changes in their IQ, even after a long follow-up. In 92 % of patients there is a behavioral improvement. Satisfactory results are encountered if intelligence was normal before epileptic encephalopaty and if antiepileptic drugs were suspended after surgery. In those patients with right hemispherotomy an important deficiency of visuospatial functions and especially visualperceptual reasoning is described.

Conclusion: Here we refer the neuropsychological follow-up of our patient, with the aim of evaluating neuropsychological function development and how much it is conditioned by the crowding effect.

P03

LONG-TERM CARDIOVASCULAR SAFETY OF FENFLURAMINE HCL IN THE TREATMENT OF DRAVET SYNDROME: INTERIM ANALYSIS OF AN OPEN-LABEL SAFETY EXTENSION STUDY

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Objectifs: Fenfluramine (FFA) has demonstrated superior efficacy vs placebo for convulsive seizure (CS) frequency reduction in children and young adults (2-18 years) with Dravet syndrome (DS) in recent Phase 3 clinical studies. FFA was withdrawn from use for weight loss in 1997 following reports of cardiac valvular heart disease (VHD) and pulmonary hypertension (PAH) in obese adults treated with ≥60 mg/day. We report an interim analysis of FFA's cardiovascular safety in a long-term open label extension (OLE) study.

Methods: Patients with Dravet syndrome successfully completing any Phase 3 trial were eligible for this open-label extension (OLE) study. Patients with current cardiac VHD, pulmonary arterial hypertension, or any aortic or mitral valve regurgitation had been excluded from entering Phase 3 trials. All OLE patients were started on FFA at 0.2 mg/kg/day, after 4 weeks doses could be uptitrated 0.2 mg/kg/day every 2 weeks based on efficacy and tolerability, to 0.8 mg/kg/day or 0.5 mg/kg/day if taking concurrent stiripentol (maximum 30 or 20 mg/day respectively). ECHOs were performed at study baseline, Week 6, then 3-monthly to assess cardiac valve function and pulmonary artery pressure. Cardiac VHD was defined as the presence of ≥ moderate mitral regurgitation and/or ≥ mild aortic regurgitation; pulmonary hypertension as pulmonary artery systolic pressure > 35 mm Hg.

Results: 232 patients enrolled by March 13, 2018 and had received ≥ one FFA dose. Twenty-two (9.5%) patients discontinued treatment for: lack of efficacy (16), adverse event (1), death (1, SUDEP), physician decision (1), subject (2) or caregiver (1) withdrawal. 128 (55.2%) patients were male, mean age 9.1±4.7 years. The median FFA treatment duration was 256 (58-634) days. No patient demonstrated cardiac VHD or PAH during the study. Most common findings were intermittent and transient physiologic/trace valve regurgitation, also seen in normal healthy children and young adults.

Conclusion: These long-term safety results demonstrate no development of cardiac VHD or pulmonary hypertension after daily treatment with FFA for <21 months in Dravet syndrome patients. Together with Phase 3 efficacy data, fenfluramine appears to have a positive benefit-risk profile in this patient population.

Funding: Zogenix, Inc.

P04

FENFLURAMINE REDUCES CONVULSIVE SEIZURE FREQUENCY IN DRAVET SYNDROME PATIENTS RECEIVING AN AED TREATMENT REGIMEN CONTAINING STIRIPENTOL: A PHASE 3, RANDOMISED, PLACEBO-CONTROLLED CLINICAL TRIAL

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Objectifs: Fenfluramine (FFA) has been recently shown in a Phase 3 study to reduce convulsive (tonic)-clonic seizure (CS) frequency compared to placebo in Dravet syndrome (DS) patients taking an AED regimen not including stiripentol (STP). This second Phase 3 study compared FFA to placebo in DS patients receiving treatment including STP but still uncontrolled.

Methods: DS children and adolescents (2 to 18 years) receiving AED treatment including stable STP doses were eligible. Patients with ≥6 CSs during the 6-week baseline randomly received FFA 0.5 mg/kg/day (max 20 mg/day) or placebo; FFA 0.5 mg/kg/day provides comparable exposure to 0.8 mg/kg/day without STP. Following 3-weeks blinded titration (T), patients maintained their randomized dose for 12 weeks (M). Seizures (number and type) were recorded daily. The primary efficacy endpoint was the CS frequency change on FFA vs placebo during T+M periods vs baseline.

Results: 87 patients, median age 9 (2-19) years were randomized. Mean baseline CS frequency (both arms) was about 25 convulsive seizures/month. FFA-treated patients (n=43) achieved 54.7% greater reduction in monthly CS frequency vs placebo (n=44, P<0.001). FFA was also superior in both key secondary endpoints. 53.5% of patients demonstrated a ≥50% reduction in monthly CS on FFA vs 6.8% on placebo (P<0.001). Median longest seizure-free intervals were 22 days on FFA vs 13 days on placebo (P<0.005) with a ≥75% reduction in monthly CS frequency in 32.6% of patients on FFA vs 2.3% on placebo (P=0.004). FFA was generally well tolerated. No echocardiographic or clinical signs of cardiac valvular heart disease or pulmonary hypertension were seen.

Conclusion: FFA demonstrated robust efficacy in this study in DS patients on a stable AED regimen including STP. FFA was generally well tolerated, with no cardiac effects. FFA may represent an important, effective new treatment for DS patients.

Funding: Zogenix, Inc.

P05

FENFLURAMINE IN DRAVET SYNDROME: EFFECT ON CONVULSIVE SEIZURE FREQUENCY IN PATIENTS WHO FAILED TREATMENT WITH STIRIPENTOL PRIOR TO STUDY 1

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Objectifs: To assess the effect of fenfluramine (FFA) on frequency of convulsive (tonic)-clonic seizures (FCS) in a subset of Dravet syndrome (DS) patients in a phase 3 clinical trial (Study 1) who had previously been treated with stiripentol (STP).

Methods: Following a 6-week baseline period, patients who discontinued STP prior to entry in study 1 were randomized 1:1:1 to placebo (n=16), FFA 0.2 mg/kg/day (n=20), or FFA 0.8 mg/kg/day, maximum dose 30 mg/day (n=22) and treated for 14 weeks, including an initial 2-week titration period. Number and type of seizures were recorded daily in an electronic diary.

Results: 58 patients, mean age 9.7 years (range, 2-18), met the criteria for this analysis. FFA 0.8 mg/kg/day showed a 60.8% reduction in mean monthly FCS vs placebo (p=0.002). Seventy-three percent of subjects in the FFA 0.8 mg/kg/day group achieved ≥50% reduction in FCS (p=0.006) and 50% achieved ≥75% reduction in FCS (p=0.036). Longest median seizure-free intervals were 24.5 days (0.8 mg/kg/day, p=0.003), 18 days (0.2 mg/kg/day, p=0.012), and 9 days (placebo). Compared with placebo, ZX008 0.8 mg/kg/day-treated subjects were more likely to be rated much or very much improved by parents/caregivers (41% vs 6%, p=0.012) and investigators (64% vs 6%, p<0.001). FFA was generally well tolerated.

Conclusion: FFA provided robust improvement in FCS in subjects with DS who had previously used a current antiepileptic regimen that contained stable doses of stiripentol. FFA may represent an effective new treatment option for these patients with DS.

Funding: Zogenix, Inc.

P06

PELIZAEUS MERZBACHER-LIKE DISEASE: CLINICAL AND RADIOLOGICAL ASPECTS OF A TUNISIAN SERIES

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Objectifs: To report the clinical and radiological features of patients with PMDL compared to PMD patients.

Background: Pelizaeus Merzbacher-like Disease (PMDL) is a rare hypomyelinating leukodystrophy with autosomal recessive inheritance linked to a homozygous mutation of the GJC2 gene. The preservation of cognitive and motor function distinguishes it from X-linked Pelizaeus Merzbacher disease (PMD) resulting from mutation of the PLP gene.

Methods: Nine children (6 unrelated families) carrying genetically confirmed PMDL, followed in our department. Their symptoms, physical examination, brain MRI and neurophysiological data were analyzed.

Results: The nine children (7 boys and 2 girls) were born from a consanguineous marriage. Congenital nystagmus was noted in all patients. They had all developed psychomotor retardation. Epilepsy was noted in two patients. Examination showed nystagmus, axial hypotonia, cerebellar ataxia in all patients, spastic tetraparesis in 6 cases, and upper limb dystonia access in 3 cases. Brain MRI showed diffuse hypomyelinating leukodystrophy in all patients and involvement of the brainstem in 6 cases. The ENMG did not show any anomalies. Visual evoked potentials showed severe demyelinating optic neuropathy in one case. Auditory evoked potentials were altered in 2 cases. The genetic study confirmed the diagnosis of PMDL by showing different homozygous mutations of the GJC2 gene in all patients with a recurrent mutation in patients from the North West.

Conclusion: Our study illustrates the prevalence of PMDL compared to the PMD because of the importance of consanguinity in our population. Our patients had a more severe clinical phenotype than reported in the literature. Brainstem injury may represent a distinctive radiological element with PMD. We found a recurrent mutation in our patients from northwestern Tunisia.

P07

ASSESSMENT AND MANAGEMENT OF PAIN IN CHILDREN WITH CEREBRAL PALSY

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Objectifs: The aim of this work is to evaluate the painful manifestations of children followed for cerebral palsy and to propose an adequate treatment.

Background: Pains represent one of the most common problems experienced by children with cerebral palsy (CP). It has a negative impact on daily life. As a result, assessment of pain is important to improve the quality of life.

Methods: We conducted a prospective study including 30 children with Cerebral Palsy followed in the Department of Child and Adolescent Neurology of the National Institute of Neurology of Tunis. To detect and assess pain, the San Salvadour scale adapted to the Tunisian dialect (DESS) was used. This scale, applicable from 2 years to adulthood, has 10 items. The score is between 0 and 40.

Results: There were 30 children (20 boys and 10 girls). The average age was 6.8 years old. 83% of the children had pain. 35% of them were aged less than 4 years old. There was a male predominance with a sex ratio of 1.5. The average pain score was 14/40. Pain was moderate in 77% of patients and severe for the rest of children. It mainly affected the lower limbs in 80% of patients. In the majority of cases, bone deformities and tendon retractions were the cause of pain. Osteoporosis and associated fractures were found in 2 children. Pains related to medical care and physiotherapy were present in 25% of cases. From therapeutic standponint, physical therapies to relieve pain were performed in 20 children. 29 children received analgesic treatment from level I and one child were treated by analgesic from level III. A spinal surgery has been proposed in a patient with a disabling scoliosis relay with the bisphosphonates for analgesic purpose.

Conclusion: Pain accompanies children with CP and affects their quality of life. Pain management is a necessary part of the treatment and it must be multidisciplinary.

P08

MALFORMATIONS OF CORTICAL DEVELOPMENT: CLINICAL STUDY OF 52 CASES

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Objectifs: The purpose of our work was to describe the different types of cortical malformations and their clinical presentations.

Introduction: Malformations of cortical development (MCD) include a broad spectrum of disorders that result from disruption of steps of cortical development during embryogenesis. They are a common cause of epilepsy and cerebral palsy.

Methods: We conducted a retrospective study in the Department of Child and Adolescent Neurology of the National Institute Mongi Ben Hmida of Neurology of Tunis, from January 2004 to July 2016. We collected patients with a malformation of the cortical development. Clinical and paraclinical findings were collected and analyzed.

Results: We collected 52 cases. The mean age was 2.2 years (3 months-14 years). The sex ratio was 2.46. Three family cases have been identified. A personal history of perinatal distress was noted in 27% of cases and an embryofoetopathy in 4% of cases. Clinical manifestations were dominated by psychomotor retardation (81%), epilepsy (69%), mental retardation (50%) and microcephaly (31%). Epilepsy was pharmaco-resistant in 11% of cases. MCD was asymptomatic in one patient. Brain MRI showed polymicrogyria in 52% of cases, lissencephaly in 27% of cases, heterotopia in 21% of cases, pachygyria in 10% of cases, schizencephaly in 8% of cases, focal cortical dysplasia in 4% cases, and tuberous sclerosis in 2% of cases. Infratentorial anomalies were associated in 29% of the children. Genetic study concluded to Miller Dieker syndrome in one patient who had lissencephaly.

Conclusion: MDC is a major cause of infant morbidity and mortality. Brain MRI is the gold standard for diagnosis. Many genetic and environmental factors are responsible for the occurrence of these malformations. Etiological diagnosis is necessary to improve management and establish genetic counseling.

P09

NEUROLOGICAL MANIFESTATIONS IN GAUCHER DISEASE TYPE 3

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Objectifs: Rare lysosomal disease with autosomal recessive inheritance due to glucocerebrosidase deficiency. It is a multi-systemic disease with two main phenotypes: non-neuropathic form (Type 1) and a neuropathic form (Type 2 and 3). Our objectif is to describe and evaluate neurological impairment in our patients.

Materials and Methods: We report a series of 8 children admitted to Pediatrics B CHU Oran from January 2007 to September 2018, for a Gaucher disease with neurological involvement. Results: Among the 17 children (12 girls and 5 boys) followed for Gaucher disease, the neurological form is labeled in 8 children including 3 boys and 5 girls. The average age of admission in 4 cases is less than 2 years, 3 cases in early childhood and one case of school age (11 years). Clinical presentation found visceralgalygaly in all cases, a growth disorder in 5 children and neurological signs suggestive of type 3 (oculomotor apraxia in 3 cases, accesses of hypertonia in extension of the trunk and neck with an epilepsy in one case, strabismus in 4 cases, delayed psychomotor development in 3 cases, diffuse amyotrophy with weak osteo tendinous reflexes in 5 cases). In 2 cases, cerebral CT revealed cortical atrophy and decreased white matter. The genetic study confirms the type 3

Conclusion: The neurological form is not rare in our series since it affects 47% of our Gaucher patients. An enzyme replacement therapy did not improve the neurological prognosis (25% of deaths). This is most likely the typical form 3c).

P10

INFANTILE SPASMS POST- BACILLUS CALMETTE GUERIN VACCINE: A DRAMATIC PRESENTATION WITH BENIGN PROGNOSIS?

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Objectifs: Infantile spasms syndrome defines an epileptic syndrome occurring in children younger than one year. The commonest causes of infantile spasms are structural, or genetic. It's less often secondary to in born errors of metabolism, still less to brain infection. We describe the clinical case of infantile spasm secondary to cerebral abcess due to Bacillus calmette Guerin vaccination

Contenu: A 2-years-old boy was born to healthy parents, with good adaptation to extrauterine life. He was correctly vaccinated with one dose BCG at birth. Her psychomotor development was normal. Cluster of epileptic spasms began at the age of five months. Neurologic exam was normal as well as extraneurologic exam, without any fever nor meningeal syndrome. Electroencephalography (EEG) showed spasm pattern with hypsarythmia. Brain MRI showed multiple conglomerate annular lesions in the wright parietal and temporal regions with intense contrast enhancement and important edema exerting mass effect on the occipital horn of the lateralventricle. Lumbarpuncturedid not show meningitis and all Microbiological CSF and blood tests were normal. He was traited with Vigabatrin, Valproate and at first by antibiotic association anti-pyogenic germs without any improvement. That is when test anti-tubercular first line treatment was started with clinical, and radiologic amelioration.

Conclusion: Bacillus Calmette-Guerrin (BCG) is a live, attenuated strain of Mycobacterium bovis that is used to prevent tuberculosis. Disseminated mycobacterium infections following vaccine have been reported in many sites including bone, lungs, joint fluid, liver, chest wall, vascular aneurysms, and bone marrow. However, cerebral abscesses do not commonly occur, seen in less than 10% of all patients with CNS tuberculosis. That they are more common in the geriatric age group or in those with compromised immune status like in our patient, since child's immune system still weak in the first months. Therefore, abscesses are commonly found at the junction of the gray and white matter in the supratentorial compartment, which explain her potential epileptogenicity, in addition to the activation of inflammatory cascade. Which support the important role of brain inflammation in the pathogenesis of infantile spasms.

P11

CAPTURING THE MPS IIIA PATIENT AND FAMILY VOICE IN ORPHAN DRUG DEVELOPMENT TO APPRECIATE WHAT IS IMPORTANT IN MANAGING THE DISEASE AND IMPROVING QUALITY OF LIFE

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Objectifs: Mucopolysaccharidosis type IIIA (MPS IIIA) (OMIM 252900) is a rare, neurodegenerative, pediatric and lethal disease. Understanding the impact of the disease and the needs of patients and families related to treatment benefits, risks and disease burden is an important addition to assess treatment effect in clinical trials. Lysogene launched an observational study for MPS IIIA in five countries (NCT02746341), to function as a non-concurrent control for their phase 2-3 pivotal gene therapy trial (NCT03612869). The observational study includes mixed methods research using face-to-face interviews, questionnaires, and digital health technology.

Contenu: Twenty-three children were included in the study and twenty-two parents were interviewed at baseline. Data from nineteen patients and sixteen parent interviews are available at 12 months. Patient age ranged from 2 to 10 years; mean age at baseline was 61 months (range 28 – 105). Four children had been recently diagnosed and aged 2, 4, 4, and 6 years. The age range was important in providing an accurate development story covering the journey from diagnosis to the age of ten, highlighting issues that each group may face. At baseline, 43% of patients reported sleep disorder. Eight children were taking melatonin. Actigraphy showed overall stability over the course, with high inter- and intra-patient variability. The Child Behavior Checklist scores showed 30%, 50% and 60% of children had behavior scores for internalizing, externalizing and total problems above the 90e percentile, respectively. Externalizing scores increased over the study period. Data shows well-preserved Health Utility Index (HUI) scores in patients with high cognitive DQ and lower scores in patients with more advanced cognitive impairment. The parent interviews confirmed two of the main challenges of this disease: disturbed sleep and behavior.

Conclusion: Triangulation of the qualitative data with data from the QOL, sleep, cognitive and behavior questionnaires shows an overall good match between the conceptual model and questionnaire coverage for children's symptoms and impacts. Some qualitative themes are not addressed or not well addressed by the questionnaire items i.e. child's self-care or parent daily life and sleep. There may be an opportunity to assess these themes using video capture.

P12

ENCEPHALITE A AC ANTINMDA CHEZ UN NOURRISSON

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Objectifs: L'encéphalite à récepteurs(ENMDA)anti-N-méthyl-D-aspartate (NMDA) est considérée comme une maladie neurologique autoimmune sévère avec un tableau clinique spécifique .le début est progressif , après une phase prodromique simulant une virose, succède une seconde phase de crises épileptiques et de mouvements anormaux, suivi par une phase de déclin neurocognitif, de déficit moteur, des dyskinésies orofaciales, une aphasie secondaire, et un coma avec des signes Dysautonomiques.. Le diagnostic est confirmé par la détection d'anticorps antiNMDA dans le sang et dans les urines . Le cas ci-dessous illustre les données décrites de la littérature avec une bonne évolution clinique. Sa perticularité est sa survenue chez le nourrisson

Contenu: Rahaf ,fille de 3 ans, sans atcd ,admise en aout 2016 pour convulsions tonico-clonique généralisée et des mouvements choreio-athétosique .le début remontait à 1 mois marqué par une virose, et un repli sur soi .un traitement a base d'antiépileptiques et aciclovir a été instauré une aggravation a été noté à la 3ème semaine avec un déclin cognitif ,des dyskinésies orofaciales ,un mutisme akinetique , des troubles de la conscience et apparition de signes dysautonomiques .

EEG: ondes lentes diffuses avec des rythmes rapides ,avec une IRM cérébrale normale .ces derniers ont orienté le diagnostic dont le dosage d'anticorps antiNMDA dans le sang et le LCR a confirmé le diagnostic.L'évolution lente mais favorable avec récupération des fonctions cognitifs, du developpement psychomoteur et sensoriel et arret des crises sous immunglobuline mensuelle pendant 6 mois, puis 2 injections de RITUXIMAB a 15 j d'intervalle ,normalisation de EEG et disparition des anticorps antiNMDA dans le sang et le LCR avec un recul de 2 ans.Rahaf est scolarisé en école préparatoire.

Conclusion: L'encéphalite NMDA du nourrisson est évoqué devant des mouvements anormaux et une épilepsie, associé une perte des acquisitions psychomotrices, succédant à une virose, chez un enfant antérieurement sain.

L'EEG oriente le diagnostic d'encéphalite NMDA dont la détection d'AcNMDA (sang et LCR) La confirme.Le pronostic reste favorable sous rituximab.

P13

A PROPOSITION FOR A GRAPHICAL REPRESENTATION OF DIFFICULTIES AND STRENGTHS OF CHILDREN WITH SPECIFIC LEARNING DISABILITIES

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Background: Diagnosis and reeducation of specific learning disabilities are multidisciplinary: teacher, speech therapist, psychologist, psychomotor, occupational therapy, orthoptics, neuropediatrics and child psychiatrist. The communication between these actors implies a consortium on the concepts in order to build a synthesis showing the patient's difficulties and strengths to guide reeducation. This preliminary work proposes a graphical representation of the patient's profile for diagnostic and follow-up purposes.

Method: At the reference center for specific learning disabilities of Garches (CRTLA ; Centre de Référence des Troubles du Langage et des Apprentissages, Hôpital Raymond Poincaré, Garches, France), between November 2018 and January 2019, 60 consecutively received consultation request files have been studied by one investigator (RB). Relevant items to describe the patient's disability were systematically listed (RB). These items were then synthetized by two investigators (RB and ES) in 72 items dispatched in 9 categories: oral language, written language (reading / writing), mathematics, praxis, intelligence, attention, behavior, psycho-emotional and environment. These were graphically represented on an enneagram (9-sided polygon [1 for each category]). Each 9 parts of the enneagram was subdivided in numbered colored boxes corresponding to the 72 items. The colors [green, yellow, red, white] correspond respectively to [strong capacity, border, pathologic, not mentioned in the file]. Items were ordered from the center (prerequisite to the function) to the periphery (the function), and by etiologic proximity when this was relevant. The representation was then tested to evaluate 10 other consecutive files.

Results: The tool was adapted to evaluate the 10 consecutive files and could be used at the CRTLA as a basis for interdisciplinary meetings. It could also be used with profit in consultation to communicate with parents.

Conclusion: We built a schematic graphical representation of the patient's difficulties and strengths for patients facing specific learning troubles. It facilitates the interdisciplinary communication and attracts attention on the most important points: the patient's strengths on which we can drive reeducation. As is does not explain the hole complexity of the pathological situation, it has to be completed by free sentences. The construction of this tool initiates an interdisciplinary dialogue for consensus around concepts of specific learning disabilities.

P14

NEUROLOGICAL MANIFESTATIONS IN CUTIS LAXA TYPE 3A

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Objectifs: Cutis laxa, autosomal recessive, type 3a is a rare genetic condition. Eleven families have been described in medical litterature. Clinical spectrum associated to this disease includes an abundant and wrinkled skin, with skeletal anomalies, neurodevelopmental disorders and in some cases, severe neurological symptoms.

Cutis laxa type 3a (OMIM#219150) is an autsosomal recessive disease, due to pathogenic variants in *ALDH18A1* gene. This gene encodes for delta-1-pyrroline-5-carboxylate-synthetase (P5CS), which catalyses proline, ornithine and arginine synthesis.

Contenu: We report here a 8 months child, first child of a consanguineous couple, with a cutis laxa type 3a syndrome. He is carrier of a homozygous missense variant in *ALDH18A1,* c.1499G>T, p.Gly500Val.He presented an intrauterine growth retardation early during pregnancy with an oligoamnios. At age 8 months, he has a severe failure to thrive. He also presents a bilateral cataract with corneal cloudings, a ventricular septal defect and a large atrial spetal defect. He has an abundant wrinkled skin, with an important xerosis. He has repeated skin infections.Neurologically, he presents a four limbs spasticity with tremulations. Brain MRI shows megadolicho vessels, especially on willis circle, a diffuse cerebral atrophy and white matter signal anomalies.

Conclusion: This case report enlarges the neurological aspects of cutis laxa type 3a and provides a better characterization of this syndrome.

P15

NEURO-BEHAVIORAL PHENOTYPES OF PATIENTS WITH FETAL ALCOHOL SPECTRUM DISORDER (FASD)

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Objectifs: To describe neuro-behavioral phenotypes of patients with Fetal Alcohol Spectrum Disorders (FASD) and the specific support needed for these patients

Contenu: Exposure to alcohol during pregnancy is a risk factor for multiple developmental abnormalities including the central nervous system of the fetus and the developing child. Some of them cause long-term disabilities with negative consequences for the quality of life of both patients and their families. Exposure to alcohol during pregnancy is the first preventable cause of non-genetic mental impairment and social maladjusment. In France, 1/1000 live births of Fetal Alcohol Syndrome (FAS) and 1 in 100 live births of Fetal Alcohol Spectrum DIsorders (FASD) - approximately 8000 children / year. In Reunion Island, 140 children / year at least are born with brain abnormalities caused by alcohol.

We propose a descriptive retrospective analysis of the cognitive and behavioral profiles of 49 patients with FASD after a multidisciplinary assessment at the first in France Diagnosis Center for Fetal Alcohol Spectrum Disorders from July 2017 to December 2018.

49 patients with FASD were assessed, from whom 37% (N = 18) with complete Fetal Alcohol Syndrome, 27% (N = 13) with partial Fetal Alcohol Syndrome, 37% (N = 18) with neurodevelopmental disorder related to fetal alcohol, 14% (N = 7) with FASD comorbid to a genetic abnormality. Except 2 patients, all had cognitive or instrumental disorders, including intellectual disability, learning disabilities, executive disorders, memory disorders or visuospatial disorders. For 93% (N = 46), self-regulation functions were impaired with emotional dysregulation, attentional deficit, impulsivity and other psychiatric disorders. 98% (N = 48) had a secondary disability impacting school education or social adjustment skills that required specific support.

Conclusion: All patients with FASD have multiple cognitive and behavioral disabilities with frequent psychiatric comorbidities leading to an adaptative functioning impairment and negative consequences on school education and social skills.

These findings highlight how essential it is to have an early diagnosis with a systematic functional evaluation in order to offer personalized early support tailored to each child's phenotype. This care would help to change the trajectory of children with FASD and reduce over-handicaps by empowering families, social and educational environment, as well as developing partnership of healthcare actors around these patients and families.

P16

ZERO INCIDENCE OF ADENO-ASSOCIATED VIRUS SEROTYPE 9 (AAV9) ANTIBODIES IN A COHORT OF SPINAL MUSCULAR ATROPHY TYPE 1 (SMA1) PATIENTS SCREENED IN STR1VE, A PIVOTAL PHASE 3 STUDY OF AVXS-101

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Objectifs: SMA1 is a rapidly progressing, debilitating neurodegenerative disease caused by bi-allelic deletion/mutation of the survival motor neuron 1 (*SMN1*) gene, resulting in motor neuron loss, muscle weakness, respiratory failure, and early death. AVXS-101 is a recombinant, replication-incompetent AAV9-based investigational gene-replacement therapy (GRT) containing a copy of the human *SMN* gene and is administered as a one-time intravenous infusion. AVXS-101 GRT treats the genetic root cause of SMA and is designed for immediate and sustained expression of SMN protein, allowing for rapid onset and durable therapeutic effect because it targets non-dividing neurons. AVXS-101 showed dramatic improvements in survival, motor function, and motor milestone achievement in SMA1 patients. No formal studies assessing AAV9 antibody prevalence in SMA infants have been performed, but AAV9 antibodies are thought to be rare in infants.

Contenu: STR1VE is a phase 3, pivotal study of AVXS-101 in symptomatic SMA1 patients <6 months of age at the time of dosing (NCT03306277). For eligibility, AAV9 antibody titers were measured by enzyme-linked immunosorbent assay; patients with antibody titers >1:50 were excluded. Among 25 infants (median age 3 months, range <1–5.6) screened for AAV9 antibodies, none manifested exclusionary antibody titers.

Conclusion: Consistent with experience from the AXVS-101 phase 1 trial (NCT02122952), where only 1 of 16 patients was excluded due to elevated AAV9 antibody titers, results from STR1VE suggest elevated AAV9 antibody titers are a rare event that should not impact the ability of the vast majority of symptomatic SMA infants to receive AAV9-based GRT. An ongoing trial assessing AVXS-101 in pre-symptomatic patients with SMA (NCT03505099) will provide information on AAV9 antibody levels in newborns younger than 3 months of age, who may be passively exposed to maternal AAV9 antibodies.

P17

OPHELIA SYNDROME: LIMBIC ENCEPHALITIS WITH MGLUR5 ANTIBODIES COEXISTING HODGKIN'S LYMPHOMA

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Objectifs: Auto-immune diseases are often associated with Hodgkin's lymphoma. Classically the lymphoma is known, but sometimes, diagnosing anti mGlutR5 encephalitis may anticipate the diagnostic of a cancer and lead to potentially highly effective treatment option.

Contenu: As in the famous story of Shakespeare (deception love of Ophelia by Hamlet), an eleven year old girl suffered from acute neuropsychiatric abnormalities : headaches, immediate memory disorders, temporal disorientation and recent changes in behavior.

She has no fever and her clinical examination was strictly normal within organomegaly. No biological inflammatory syndrome. Lumbar puncture found pleocytosis with 28 elements in the cerebrospinal fluid (CSF). Protein and glucose levels were normal in CSF. We made the diagnosis of lymphocytic meningitis but various viral PCRs were negative. Extensive testing for infectious encephalitis was unremarkable. We found in the CSF oligoclonal IgG bands (CSF), which was not observed in corresponding serum. Electroencephalography and MRI were unremarkable. Antibodies to mGluR5 in CSF were returned as positive. Tep-Scann imagings show two adenopathies in sus-diaphragmatic. Biopsy confirms the diagnosis of scleronodular hodgkin lymphoma. With the classical protocol treatment for this type of blood disease, neurological evolution was spontaneously favorable with a good recovery in 15 days.

mGluR5 is found on post-synaptic terminals of neurons and microglia and is expressed primarily in the hippocampus and amygdala. The mGlur5 antibody would cause more neuronal functional imbalance than real neuronal death.

Conclusion: This case highlights the difficulties in diagnosing this type of encephalitis: the CSF shows a little pleocytosis, but the MRI and the electroencephalogram were normal. So, a high index of suspicion is needed to avoid missed diagnosis. In patients with unexplained encephalitis, testing for antibodies to mGluR5 in CSF and serum should be considered and there is a reasonable index of suspicion of neoplasic syndrome. Treatment of lymphoma most often allows a spontaneous recovering of encephalitis.

P18

A NOVEL INF2 MUTATION IN AN ITALIAN GIRL WITH CHARCOT-MARIE-TOOTH, NEPHROPATHY AND BIPOLAR DISORDER

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Objectifs: Charcot-Marie-Tooth (CMT) disease E is an autosomal dominant intermediate type characterized by the neurologic features of Hereditary Motor and Sensory Neuropathy, including distal muscle weakness, atrophy and distal sensory loss, and the features of Focal Segmental Glomerulosclerosis (FSGS), including proteinuria, progression to end-stage renal disease, and a characteristic histologic pattern on renal biopsy. The common mechanisms underlying the neuropathy and FSGS remains unknown. INF2 encodes a formin protein that interacts with the Rho-GTPase CDC42 and myelin and lymphocyte protein (MAL) that are implicated in essential steps of myelination and myelin maintenance. It was therefore hypothesized that INF2 may be responsible for cases of Charcot–Marie–Tooth neuropathy associated with FSGS. To date, there are only 7 known gene mutations found in relation to dominant intermediate Charcot-Marie-tooth disease (CMT E). These are: INF2, Cys104Arg; INF2, Cys104Phe; INF2, Cys104Trp; INF2,Leu128Pro; INF2, Leu132Arg; INF2,9-BP DEL,NT490 and INF2, c.2659GA; p.E887K(het.).

Contenu: A seventeen-year-old girl presented an “atipycal” Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) from the age of 10 years, characterized by abolition of deep tendon reflexes in the lower limbs and, especially in the autumn and winter, walking difficulties, limited legs function and muscle wasting. She has been initially treated with monthly pulse IVIg with partial benefit. Then, at 16 years, she also started to show an isolated proteinuria and IgA nephropathy was found. There was no arterial hypertension. IVIg treatment was suspended. She was treated with an ACE inhibitor and oral prednisone has been taken for 6 months with reduction of proteinuria. Gene analysis identified a novel heterozygous mutation c.593T>C (p.Leu198Pro): the amino acid Leucine is replaced with a Proline in position 198 of the protein, in the IFN2 gene located on chromosome 14q32. The novel mutation is de novo one. Steroids and IVIg treatment were stopped. To date, CMT is incurable without the usage of symptomatic drugs. She has presented also attention deficit and hyperactivity symptoms since childhood. In adolescence bipolar disorder was diagnosed. The nephrologist denied a drug therapy at that time, but cognitive behavioral therapy led to a good stabilization of the psychopathology. In recent literature cases of CMT with mental disorders are not described.

Conclusion: The novel INF2 mutation (p.Leu198Pro) is not described yet in literature and a correlation to CMT type E could exist. Further research on psychological manifestations in neuropathies is needed.

P19

INTRAFAMILIAL CLINICAL VARIABILITY OF 16P13.11P12.3 DELETION

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Objectifs: In most cases of genomic disturbances it is expected that symptomatology will be similar between cases furthermore if they occur within the same family. We report here a family case of epilepsy and cognitive difficulties related to 16p13.11 deletion in which we found several differences of expression between members.

Contenu: MM was born from gemellar pregnancy without any complication. By the age of 6-7 months he started to exhibit flexor spasms. They were controled by Vigabatrin followed by Topiramate. He became free of seizures but had an obvious developmental delay on both motor and langage performances. Now He still needs multidisciplinar rehabilitation program. His brother never showed any seizures neither delay. The oldest sister EM first had febrile seizures at the age of 2Y and a « spell » at 8 Y. A diagnosis of generalised epilepsy + atypical absences was made at the age of 12. This has been preceded by a dyscalculia and an attention deficit disorder as well as anxiety. She has been treated by Valproate then Keppra. Now seizure free she is following an adapted scholar program. The youngest sister RM had a first tonic seizure by the age of 8Y. Parents also observed « absences ». She also complained of headache and memory difficulties associated to dyspraxia. She seems actually well covered with Keppra. All Neuroradiological exams as well as biologies were always normal, but molecular biology revealed in all a 16p13.1p12.3 deletion including several genes (ABCC6, NEDE1, XYLT1) known as related to epilepsy. This deletion seems to have been inherited from the mother who so far does not present any epilepsy neither cognitive difficulties.

Conclusion: 16p13.11p12.3 deletion seems responsible in this family for epilepsies and cognitive disabilities. Their intensity and expression are anyway variable. This may be due to variation of the penetrance. This contrast also with the benign signification of the duplication within the same region.

P20

NEONATAL VISUAL ASSESSMENT GRID (NAVEG) A NEW TOOL FOR DETECTING PRETERMS AT RISK OF BRAIN LESIONS: THE VALIDATION STUDY

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Objectifs: Visual function plays a central role in early development and can be an indicator of newborns neurological status. Prematurity is risk factor for visual impairment due to a greater brain vulnerability. In a previous paper the NAVEG visual grid was applied to a cohort of newborns correlating the visual profile to the neurological evaluation and the US findings. The aim of this study was to validate NAVEG visual grid as an assessment tool in the population of preterms, and to give a preliminary evaluation of NAVEG as an indicator of potential neurological impairment.

Contenu: A group of preterms (111) from NICU of Spedali Civili of Brescia had been consecutively enrolled from Febrauary 2018. All subjects are ≤ 32 weeks gestational age. Exclusion criteria were the presence of severe genetic diseases and the evidence of ROP (≥2). All preterms were evaluated at term age and underwent NAVEG visual assessment, US scan and Neurological examination.The sample consisted of 111 newborns, of which 55 (49.6%) females. Pregnancy course was abnormal in 97 (88.2%), and in 89 cases (80.9%) delivery was made by C-section. In most of the newborns, weight at birth was adequate to their gestational age (73, 68.9%), while 32 (30.2%) were small for gestational age and only one (0.9%) was found to be large for gestational age. 16 newborns (14.6%) had a positive familiar history of neurological diseases. After US scanning, 20 (21.1%) were found to have a transient hyperechogenicity and parenchymal lesions were observed in 2. For the primary aim of the study, according to the study protocol, the data will be analyzed through Exploratory Factor Analysis in order to assess the latent dimensions of NAVEG. For the co-primary objective of assessing NAVEG's capability to identify potential cases of neurological lesion, a Multiple Correspondence Analysis will be applied, using as a passive explanatory variable different gold standards of neurological status (ENTAT examination, US scanning, MRI scanning). In addition, the latter analysis will provide concurrent evidence of validity.

Conclusion: Considering to the validation study presented, we propose NAVEG as a screening test for detecting prterms at risk of brain lesions since the first days of life.

P21

MUTATION IN POLR3K CAUSE HYPOMYELINATING LEUKODYSTROPHY AND ABNORMAL RIBOSOMAL RNA REGULATION

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Objective: Identification of genetic cause in 2 consanguineous families with hypomyelinating leukodystrophy.

Methods: Homozygosity mapping combined to whole-exome sequencing in consanguineous families. Determination of the mutation consequences by studying the structural change of the protein and by RNA analysis of patient's fibroblasts.

Results: We identified a biallelic mutation in a gene coding for a Pol III specific subunit, POLR3K (c.121C>T/p.Arg41Trp) that cosegregates with the disease in two unrelated patients. Patients expressed neurological and extraneurological signs found in POLR3A and POLR3B related leukodystrophies with a peculiar severe digestive dysfunction. The mutation impaired the POLR3K-POLR3B interactions resulting in zebrafish in abnormal gut development. Functional studies in the two patients' fibroblasts revealed a severe decrease (60-80%) in the expression of 5S and 7S ribosomal RNAs in comparison with control.

Conclusions: These analyses underlined the key role of ribosomal RNA regulation in the development and maintenance of the white matter and the cerebellum as already reported for diseases related to genes involved in transfer RNA or translation initiation factors.

P22

EARLY INTERVENTION IN PRETERM VLBW INFANTS: AN EXPERIMENTAL TRIAL WITH AN EASY AND LOW-COST PROGRAM

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Background: The aims of this project are to design an easily feasible intervention protocol to sustain parents of preterm babies in their role during Neonatal Intensive Care Unit (NICU) hospitalization and to evaluate the effect of this early parenting intervention on maternal caregiving behaviour, on maternal well-being and on infants' developmental outcome.

Methods: We enrolled newborns hospitalized at Policlinico San Matteo NICU of Pavia (Italy) from January 2015 to December 2016 born at gestational age ≤32 weeks and/or with birth weight ≤1500 g with healthy parents with a good knowledge of spoken and written Italian and we divided them into experimental and control groups (standard care) according to birth order. The early intervention protocol consists of two group meetings with mothers and four individual meetings with the mother, her baby and a neurodevelopmental therapist, whose role is to support the mother in infant care. Information booklets regarding characteristics and development of preterm babies are given to all women. Self-administered questionnaires have been used to assess maternal stress, post-natal depression, maternal postnatal attachment, and perceived nurse and social support in the NICU, at term age and at 3 months of corrected age. The infants performed neurological examination, General Movement (GM) recording and the NNNS Attention (Orientation) subscale. The mother-infant relationship has been assessed using the Global Ratings of Mother Infant Interaction Scale.

Results: There are no significant differences in questionnaire results filled by mothers between the two groups. There are no significant differences in babies' neurological examination, in GMS' scoring and in the NNNS score. Analysing with a regression model three variables (group allocation, presence in NICU and mother intrusiveness) we find that in the control group greater presence in NICU predicts greater intrusiveness, while in the experimental group this effect is not detected.

Conclusions: The intervention made by this small, easy, low cost and easily reproducible program appears to have a protective effect in changing maternal attitude towards their preterm babies especially on maternal intrusiveness. Helping mothers to better understand their infants and supporting the parental function in the difficult initial weeks after preterm birth could modify the parental attitude and the relationship with the baby.

P23

HETEROGENEOUS PHENOTYPE EXPRESSION OF AICARDI GOUTIÈRES SYNDROME WITH THE SAME RNASEH2B/AGS2 GENE HOMOZYGOUS MUTATION

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Objectifs: The study aims at describing the phenotype associated with the same mutation (A177T) in RNASEH2B/AGS2 gene, the most frequent genetic mutation found in the European AGS cohort collected by IAGSA (International Aicardi Goutières Syndrome Association).

Background: Aicardi-Goutières Syndrome (AGS) is a rare genetic disorder with predominant neurological involvement. Originally the clinical phenotype was described as a severe condition with onset in the first year of life. Growing understanding of the disease, particularly from a genetic standpoint, allowed for a wider clinical spectrum to be described in association with ASG. Mutations in seven genes (TREX1, RNASEH2B, RNASEH2C, RNASEH2A, ADAR1, SAMHD1, and IFIH1) have been defined as pathogenic for AGS to date.

Methods: We reviewed the clinical records from all patients (n=20) with A1771T (c.529G>A; rs75184679) homozygous missense mutation in the exon 7 of the RNASEH2B gene from the AGS cohort referred to IAGSA at IRCCS Mondino Foundation in Pavia (Italy). The genetic tests have been performed using before Sanger sequencing (12 patients) and after Next Generation Sequencing (8 patients). About Sanger sequencing technique we have used standard protocol with Big-Dye Terminator v3.1 sequencing kit (Applied Biosystems) and ABI 3130 Genetic Analyzer (Applied Biosystems). NGS has been performed with Nextera Rapid Capture (Illumina), according to the manufacturers' instructions using a panel (82 calcification associated genes) including all seven AGS genes and RNASET2 gene. Duplications or deletions in AGS genes were analyzed with SALSA MLPA P388-A2 Aicardi-Goutières syndrome probe mix kit (MRC-Holland, Amsterdam). The interferon signature was performed on 10 patients (Rice et al., 2017).**Results:** Seven patients (35%) showed a mild phenotype. They all presented infantile onset except for one with disease manifestations after 1 year of age. The thirteen (65%) severe patients showed a classic phenotype with or without extraneurological involvement.

Conclusion: The cohort carrying the homozygous A177T RNASEH2B mutation was found to show a very heterogenous clinical picture with a phenotype ranging from a severe spastic-dystonic tetraparesis to a mild hemiparesis. In our experience mild AGS patients overall are more frequently associated with this homozygous mutation. Therefore, we hypothesized the protective or negative influence of other genetic factors that could impact on trascriptome profile. Indeed, in-depth trascriptomics studies should be carried out to define mRNAs profile and epigenetic regulatory RNAs to understand the different phenotypes.

P24

NEONATAL ENCEPHALOPATHY CAUSED BY RARE GENETIC MUTATIONS: A CASE OF TETRASOMY 9P

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Tetrasomy 9p is a very rare chromosomal disorder that was first described in 1973. People with this syndrome usually have a small extra chromosome made up of two copies of part of chromosome 9. This condition appears to result from de novo errors very early in embryonic development that occur for unknown reasons. The symptoms of Chromosome 9, Tetrasomy 9p may vary greatly in range and severity from case to case. Associated abnormalities may include mild growth retardation before or after birth, typical facial features and abnormal skeletal malformations of skull (microcephaly or macrocephaly), hands, fingers, arms or legs, moderate to severe psychomotor or mental retardation with hypotonia. In addition, the disorder may be characterized by various visceral abnormalities, such as malformations of heart, kidneys, urinary or genital systems. We describe the case of a two-year-old girl, the only child of non-consanguineous healthy Moroccan parents. The girl was born by spontaneous vaginal delivery, at term. Ultrasound scan during the second trimester detected intrauterine growth retardation. BW was 2045 g and occipitofrontal circumference was 28 cm. Physical examination at birth revealed large anterior fontanelle and facial dysmorphisms in association with abnormal position of left lower limb due to femoral head malposition. For the presence of psychomotor delay and axial hypotonia a brain MRI was performed, showing wide cisterna magna, ventricular dilation and corpus callosum hypoplasia. Cardiac USS revealed mild mitral insufficiency. Auditory brain response revealed deafness. Standard cytogenetic investigations on peripheral blood demonstrated the presence of an extra chromosome. Whole genome CGH array showed a tetrasomy 9p (arr 9p24.3p.13.1). We present this case because tetrasomy 9p is a rare genetic mutation, less than 100 cases in literature. The presence of deafness is due to malformations of external (narrow external ear canals and excess wax in the ear canal) and middle ear. Chromosome 9 contains between 900 and 1,200 genes. Many of these genes play a crucial role in the development of body organs and sustaining functional activities. This case underlines the importance of performing genetic investigations in all newborns and babies with dysmorphic features associated with psychomotor delay or congenital malformations.

P25

HYPOXIC-ISCHEMIC ENCEPHALOPATHY: PREVALENCE AND PROGNOSIS IN A TUNISIAN NEONATAL UNIT

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Objectifs: The aim of the study was to determine the prevalence of neonatal hypoxic-ischemic encephalopathy (HIE) in infants born in a birth asphyxia context and to evaluate its prognosis.

Methods: We conducted a retrospective descriptive study between January 2016 and December 2017 in the NICU of Charles Nicolle Hospital of Tunis. We included all full-term infants hospitalized for BA. The clinical diagnosis was based on the existence of an obstetrical event, an Apgar score < 7 at fifth minute and the presence of neurological signs. We evaluated the short-term consequences of BA on newborns: death, multiorgan failure, neonatal HIE.

Results: During the study period, 46 out of 5488 at term live births (0.83%) presented BA. Sex ratio was 0.52. Acute fetal distress was noted in 60.9 % of cases. Amniotic fluid was meconial in eight cases. Caesarian rate was at 47.8%. Mean of Apgar score at five minutes was 5 [0 - 6]. Infants were at grade I by Sarnat: n=31 (67.4%), garde II: n=7 (15.2%) and grade III: n=8 (17.4%). Associated morbidities to HIE were: respiratory discomfort (65.2%), pulmonary arterial hypertension (8.7%), and hemorrhagic syndrome (8.7%). Biological abnormalities were dominated by: metabolic acidosis (71.7%), hepatic cytolysis (50%), kidney failure (21.7%) and disseminated intravascular coagulation (8.7%). Transfontanellar ultrasound showed abnormalities in eight infants. MRI was done in six cases and was pathological in four infants. Prognosis was favorable in 34 cases (73.9%) with a normal exam at day 7 of life with a satisfactory neurological development in most cases. The mortality rate was 17%.

Conclusion: Our results showed an intrapartum asphyxia rate of 0.8% higher than the one widely recorded of 0.5%. The high associated morbidity and mortality recall the need to strengthen prevention by an efficient and satisfactory resuscitation.

P26

CEREBRAL VASCULAR THROMBOSIS IN NEWBORN INFANTS: ABOUT THREE CASE REPORTS

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Objectifs: Newborns infants have the highest risk for thrombosis among pediatric patients. Cerebral vascular thrombosis (CVT) may be caused by underlying disease, systemic anomalies or using indwelling central catheters. We report three cases of CVT in newborn infants which occurred in different contexts.

Contenu: Case 1: A term baby boy born of a 38-year-old primigravida mother. Parents were non-consanguineous with no family history of heritable vascular disorders. Newborn examination found a port-wine stain on left side of face along the forehead and the distribution of the ophthalmic division of the trigeminal nerve and a diffuse purple reticular pattern over the whole body, the back, trunk, arms, and legs. Cerebral MRI revealed thrombophlebitis of the superior longitudinal sinus. CTV associated with facial infantile hemangioma and cutis marmoratatelangiectaticacongenita was a part of Sturge Weber Syndrome.

Case 2: A preterm baby boy born at 36 weeks' gestation of a 40-year-old multipare mother. No family history of heritable vascular disease. He was admitted on day 16 of life for neonatal meningitis revealed by generalized seizures. Cerebral MRI showed a cerebral thrombosis: transverse sinus and right sigmoid sinus were occluded.

Case 3: A term baby girl born of a 34-year-old multipare mother. No familial pathological history. Parents were consanguineous. The infant was admitted in NCIU on day two of life for right myoclonic hemi corporal seizures. Transfontanellar ultrasound was normal. Persistence of the seizures indicated a cerebral tomography showing brain stroke in the left sylvian territory. Diagnosis was confirmed by a cerebral angio MRI.

In all infants, CVT was treated by anticoagulants with favorable evolution. Thrombophilia assessment was negative in the three cases.

Conclusion: Cerebral vascular thrombosis may presents with different clinical features in newborns infants. The diagnosis is difficult clinically, but it should be kept on mind. Prognosis is generally favorable if treated on time.

P27

GUT MICROBIOTA COMPOSITION IN CHILDREN WITH NEW-OSET EPILEPSY: A PRELIMINARY STUDY

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Objectifs: Specific pathways linking the microbial community inhabiting our gastrointestinal tract with the central nervous system have been suggested. Indeed, the role of gut microbiota (GM), with its influence on immune mechanisms in patients with chronic neurological diseases, has recently been highlighted to be related to many of them. While there is a very small amount of studies unraveling GM composition in epileptic patients, it has been highlighted how the microbiota can alter the progression of epilepsy, in particular by modulating the release of proinflammatory cytokines. Approximately one third of patients, despite the numerous pharmacological therapies available, show drug resistance; it is, therefore, important to look for new complementary therapeutic strategies that can influence the clinical picture. This study aims to observe possible drug-driven gut community changes by characterizing pre- and post- antiepileptic drug GM.

Here we present preliminary results conducted on a dataset of 10 samples collected from 5 children affected by epilepsy, comparing their naive GM before the therapy (“naive microbiome”, NM) and after taking for at least 4 months (“in therapy”, IT) one of the most common antiepileptic drugs (Valproate, Levetiracetam, Ethosuximide). Bacterial DNA was extracted from fecal samples, sequenced via Illumina MiSeq platform and analyzed through QIIME software and specific bioinformatic pipelines.

Contenu: Overall results suggest an increased amount of Bacteroides and Faecalibacterium spp. during the therapy, whereas drug assumption seems to be related to a smaller quantity of Roseburia, Ruminococcus and Akkermansia spp.

For each pair of samples of the patients (NM vs IT), we observed a common decrease of Ruminococcus and Oscillospira spp. during the assumption of the drug. While Roseburia produces short-chain fatty acids (butyrate, in particular) and Akkermansia contributes to strengthen intestinal walls, Ruminococcus and Oscillospira help resistant starches digestion and fermentation: the decrease in the amount of these beneficial genera may indicate a dysbiosis occurring during the patients’ drug assumption.

Conclusion: These preliminary results suggest that drugs other than antibiotics could impact on gut microbiota and that they should be considered as possible environmental factors modifying the microbial community. The observed changes, in turn, might influence host response to therapy.

P28

SOCIAL COGNITION IN CHILDREN WITH DOWN SYNDROME: AN EYE TRACKING STUDY

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Objectifs: Children with Down syndrome (DS) are reported to possess considerable social capabilities. Yet individuals with DS exhibit difficulties in face affect recognition. Most recently, it has been shown that DS individuals are drastically impaired on the Face-n-Food task tapping face tuning, which is an important component of social perception (Pavlova et al., 2018). As eye tracking is a useful methodology for examination of social perception in children with neurodevelopmental disorders, for understanding the nature of this impairment, we analyzed eye movements and gazing during performance of the Face-n-Food task and compared this outcome with data in typically developing (TD) controls.

Contenu: 22 children (mean age : 13.3 years, 5 females) were enrolled in the study. All of them had confirmed diagnosis of DS: they had previously been tested positively for trisomy of chromosome 21. They were aged between 9-18 years and did not have severe visual deficits. Face tuning was studied by using the Face-n-Food paradigm, a set of food-plate images composed of food ingredients in the style of Giuseppe Arcimboldo. Gaze behavior (in terms of percentage of fixation, time spent and gaze map in the areas of interest such as mouth, eyes and outside the face) was analyzed by using eye tracking technology. Face-n-Food data and gaze behavior of 16 aged-matched typically developing children were used for comparison.

As reported earlier (Pavlova et al., 2018), DS children thresholds for recognition of the Face-n-Food images as a face were drastically higher as compared with control group: DS individuals gave the first face response on average of 7.9±0,3 SD image while healthy children saw a face on average on 3.5±1,5 SD image ($p < 0.01$, U-Mann-Whitney, two-tailed). Eye tracking data (percentage of fixation, time spent and gaze map) indicates that DS children look less at the image areas corresponding to mouth and eyes as compared to control group ($p< 0.01$, U-Mann-Whitney, two-tailed).

Conclusion: Children with DS experienced more difficulties in spontaneous recognition of non-face face-like images as a face and spent more time in gazing to the areas that are not corresponding to a key face elements. This outcome in DS individuals is rather startling because Ds individuals are believed to possess considerable socialization strengths. Eye tracking data contributes to better understanding of the origins of this deficit.

P29

DORSAL AND VENTRAL STREAM VULNERABILITY IN CHILDREN WITH DEVELOPMENTAL COORDINATION DISORDERS

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Objectifs: An involvement of dorsal stream networks has been widely described in many genetic and acquired developmental disorders, but how the integration of the two visual associative pathways, dorsal but also ventral, interact in determining motor coordination performance is not well understood.

Contenu: A group of 60 children (51 males, aged 5-12 years, mean 8.5, sd 1.8) with a diagnosis of Developmental Coordination Disorder underwent a neurocognitive protocol evaluating IQ level (WISC IV, WPPSI III), visual attention (Bell's Cancellation Task), visuo motor integration (Berry - Buktenica VMI) and global motion and form coherence (child-friendly "Ball in the grass" test – Braddick, Atkinson & Wattam-Bell, 2003; Atkinson & Braddick, 2005; Braddick et al, 2016) which evaluate dorsal and ventral stream vulnerability. A linear regression was applied to evaluate the relationship between the performance on these tasks and motor coordination abilities measured with Movement ABC test.The global score on Movement ABC is significantly related to the total IQ level, the global motion and form coherence sensitivity thresholds and the visuo motor integration skills ($F(59)= 7.35$; $p<0,001$). The measure of visual attention does not seem to be significantly related to motor coordination performance.

Conclusion: The child-friendly "Ball in the grass" test is useful to detect not only dorsal but also ventral stream vulnerability in children with developmental coordination disorders. An evaluation of both visuo-motor aspects and visual recognition skills is suggested in this clinical population.

P30

EARLY ONSET ENCEPHALOPATHY RELATED TO SLC13A5 MUTATION: A CASE REPORT

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Objectifs: Early-onset epileptic encephalopathy (EOEE) is a highly heterogeneous group of severe epileptic disorders characterized by pharmacoresistant seizures, abnormal interictal electroencephalogram neurological impairment, developmental delay, and high mortality rate. SLC13A5 is a Na-coupled transporter for citrate, expressed in plasma membrane of specific cell types in the liver, testis, and brain. Few subjects were described in medical literature with neonatal onset epileptic encephalopathy associated to hypodontia, related to autosomal recessively inherited SLC13A5 mutations. We report an additional case with neonatal epileptic encephalopathy caused by SLC13A5 mutations, and similar clinical and epileptic phenotype.

Contenu: Case report : 8 years old female, born after an unremarkable fullterm pregnancy. APGAR 10/10 with eutocic delivery. Clinical and neurological examinations were reported as unremarkable at birth. At day 1, she experienced recurrent tonic seizures with cyanosis, treated with phenobarbital and phenytoin. Seizure free for 2 weeks, then recurrence of polymorphic seizures (focal motor to bilateral tonic-clonic, focal non-motor, myoclonic, asymmetric spasms) and convulsive epileptic status. Daily seizure frequency, despite multiple pharmacological associations. At 5 years, convulsive epilepticus status in fever and admission in intensive care. At that time, she was taking phenytoin, pyridoxalphosphate and phenobarbital. Antiepileptic therapy was modified, switching phenytoin and phenobarbital to stiripentol and clobazam, with excellent results, progressive clinical improvement and seizure free. Clinical evolution was characterized by a major psychomotor delay with poor eye contact and global hypotonia without pyramidal syndrome. No facial dysmorphism was noticed, except for widely spaced teeth (gingival hypertrophy due to phenytoin?). Brain imaging, including magnetic resonance imaging with spectroscopy, infectious work-up in blood as well as urine and cerebrospinal fluid (CSF), and metabolic work-ups were not conclusive. Array- CGH was normal, NGS panel for epileptic encephalopathies showed compound heterozygous variants in SLC13A5, probably pathogenic.

Conclusion: The interest of this clinical report is on different aspects : first, it can provide further elements to the description of phenotype and outcome of a rare epileptic encephalopathy ; in addition, the surprising response to stiripentol may suggest some pathophysiological hypotheses for citrate transporter deficiency as a cause of early-onset epileptic encephalopathy.

P31

ACUTE ENCEPHALOPATHY WITH SEIZURE: AN HIDDEN HASHIMOTO THYROIDITIS

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Objectifs: First described in 1966, Hashimoto encephalopathy is a disease with no specific known cause and can occur even with normal thyroid function despite the presence of antithyroid antibodies. Affected individuals are usually euthyroid or mildly hypothyroid rarely with hyperthroid.

Contenu: An eleven year old girl, with no previous disease, but a family history of thyroiditis, suffered from acute headaches, repetitive falls, and status epilepticus with coma.

She has no fever and her clinical examination was strictly normal within organomegaly. No biological inflammatory syndrome. Lumbar puncture found a very small pleocytosis with 7 elements in the cerebrospinal fluid (CSF). Protein (0.7 g/L) and glucose levels were near normal in CSF. We made the diagnosis of lymphocytic meningitis, but various viral PCRs were negative. Extensive testing for infectious encephalitis was unremarkable.

Electroencephalography show slow wave without spike.

Cerebral TDM and MRI were unremarkable, but the radiologist notifies a particular heterogeneous aspect of thyroid on neck 'slices. An echographia shows a heterogeneous thyroid with an increased 7 mm isthmus.

We made the diagnosis of Hashimoto Thyroiditis with TSH: 21uU/ml (N 0.4 et 4.7) and T4: 7.7 pmol/l (N10-28), TPO-Ab: 17299 U/ml (N < 18), Thyroglobulin-Ab: 919 U/ml (N <37).

She benefits the classical protocol treatment: corticosteroid bolus with hormone replacement therapy. Neurological evolution was spontaneously favorable with a good recovery in 5 days.

Conclusion: This case highlights the difficulties in diagnosing this type of encephalitis : the CSF shows a little pleocytosis, but the MRI was normal. Auto-immune diseases are sometimes associated with acute Epilepsia but classically the dysimmunity is known.

Encephalitis may anticipate the diagnostic of Auto-immune diseases and lead to potentially highly effective treatment option. In patients with unexplained encephalitis, testing for TSH and TPO-Ab in CSF and serum should be considered.

P32

FEBRILE SEIZURES: AN EPIDEMIOLOGICAL AND OUTCOME STUDY OF 118 CASES

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Objectifs: Febrile seizures (FSs) are the most common seizure in childhood, occurring in 2-5% of children. Despite their frequency, there has been little unanimity of opinion regarding theirmanagement andthe need of preventive antiepileptictreatment.

The purpose of this study was to describe the epidemiological and the clinical data of FSsand to describe their outcome in order to determine the management of FSs in our population and to identify the risk factors of recurrence as well as the development of epilepsy.

Methods : A retrospective study was conducted that included 118 children with FS during a period of 2 years (2016 to 2017) in the pediatrics department of HediChaker University Hospital in Sfax, Tunisia. The patient files were first analyzed retrospectively focusing on the epidemiological, clinical, therapeutic, and evolutionary data. The age of seizure onset was defined between 3 months and 5 years. The other inclusion criteria for the study were a diagnosis of first episode of FS with no history of prior convulsions, neurological deficits, or other serious medical conditions. Simple FS was defined as a generalized seizure occurring of less than 15 min duration and without a focal deficit or recurrence in the subsequent 24 h. When one or more of these conditions were not observed, FS was considered complex.

Results : During the period of the study, 168 patients were hospitalized for first epileptic seizure , 118 (70%) of them had a first FS. The average age was 20.5 months (range: 5 months -5 years). A family history of febrile seizure was present in 30 cases (25.4%). The mean temperature at admission was 39.1 ° C. Simple FSs were found in 66 % of children, and complex FSs were observed in 34 %. The causes of fever were dominated by viral infections in 35% of cases. Sodium valproate was prescribed for 24 patients (20 %). This treatment was indicated for complex FS with prolonged duration of seizure(98.6 %). The mean duration for follow-up examinations was 1 year and 4 months, and ranged from 1 to 2 years. No deaths or permanent neurological deficits due to FSs were observed, and a total of 32 children (27 %) developed recurrent seizures which occurred in the first 6 months in 63% of cases.

Conclusion: The FSs are a common benign disorder, and no acute treatment is necessary in most cases. Therefore, education and reassurance of the families remain the mainstay of management for this disease.

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MANAGEMENT OF THE FIRST SEIZURE IN A DEPARTMENT OF PEDIATRICS: A RETROSPECTIVE STUDY ABOUT 168 CASES

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Objectifs: Seizures are one of the most common neurologic disorders in children. The pediatrician is often the first health professional notified of a child's first seizure. First seizures cause much anxiety for parents and practitioners. Our objectives were to evaluate the management of the first seizure in children in our department of pediatrics.

Methods: We conducted a retrospective study in our department during a period of 2 years (January 2016 – December 2017).

We included all children admitted for a first seizure. Data collected included: referring physician specialty, child's age, gender, developmental status, seizure type, cause of seizure, syndrome (if identifiable), presence of prior afebrile and febrile seizures, provoking factors, family history, pre/perinatal complications, results of investigations (EEG, computed tomography (CT) of the brain, and MRI) were recorded.

Results: One hundred sixty eight children were seen over the study period. The mean age of the patients was 1.69years (0.2–14 years). The causes of seizures were a provoked seizure (78%), newly diagnosed epilepsy (12.5%) and unknown causes (8.9%). The causes of provoked seizure were febrile seizures (70.2%), metabolic disorders (4.2%) and central nervous system (CNS) (2.2%). Laboratory tests were performed in all children, CT in 52 children (31%), MRI in 25 (14.9%) and lumber puncture in 40 (23.9%).

Conclusion: Initial evaluation and management should determine a cause of seizure and seek to rule out potential provocation, such as fever, CNS infection, traumatic brain injury, CNS tumor, cerebrovascular disease, or other toxic/metabolic insults. Febrile seizures are the most prevalent form of provoked seizure.

P34

ETIOLOGIES AND OUTCOMES OF STATUS EPILEPTICUS IN CHILDREN

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Objectifs: Status epilepticus (SE) is a medical emergency with significant associated mortality and morbidity. This study was conducted to determine the etiology and outcome of SE in children and to assess the predictive factors of its neurological, cognitive and behavioral prognosis.

Methods: We conducted a retrospective study of all cases of SE in pediatrics department of HediChaker University Hospital in Sfax, during a period of 8 years (2011 to 2018). The studied variables were type of seizure, duration and etiology of seizure, neurological deficit, psychomotor development and behavior, investigations, treatment and the outcome.

Results: 49 children were admitted for SE. They were aged between six months and nine years. There were no differences in gender distribution (male:26, female: 23). The most frequent etiology of SE was epilepsy (28.6%), febrile seizure (24.5%) andacute central nervous system infections (14.3%). The mean follow-up was six years and four months. The immediate mortality rate was 22.4%. The most common etiologies of mortality were refractory SE (10%), acute central nervous system infection (4%) and Rey syndrome (4%). There was deterioration in neurological status in seven children (16.3%).

Conclusion: SE is a severe life-threatening emergency with substantial morbidity and mortality. Longer duration of SE and acute symptomatic etiologies are predictors for poor outcome. A more favorable prognosis was verified in febrile status than in other etiologies.

P35

ACUTE DISSEMINATED ENCEPHALOMYELITIS: STUDY OF 15 PEDIATRIC OBSERVATIONS

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Objectifs: Acute disseminated encephalomyelitis (ADEM) is a primarily pediatric, immune-mediated disease characterized by demyelination and polyfocal neurologic symptoms that typically occur after a preceding viral infection or recent immunization.

The aim of our study: To determine the frequency, etiology (viral infection or vaccination), presenting signs and symptoms, response to therapy, complication and course of acute disseminated encephalomyelitis (ADEM) in our hospitals.

Methods: We conducted a retrospective study including all children who were hospitalized in the general pediatric ward of the HEDI CHAKER CHU in sfax for ADEM over a 15-year period (2004-2018). The clinical, paraclinical, therapeutic and evolutionary characteristics have been analyzed and discussed.

Results: 15 children (11 boys and 4 girls) were included in this study. The average age of onset was 7.5 years. In the state phase, headache was noted in 7 patients, gait disturbance in 5 cases, cranial nerve disease in 2 cases, bladder retention in 2 cases, seizure in 1 case, behavior disorder in 1case. Initial brain MRI showed white matter involvement in 15 cases, basal ganglia in 5 cases, brainstem involvement in 6 cases, and spinal cord involvement in 4 cases. 11 children received high-dose IV methylprednisolone followed by oral corticosteroid therapy. The evolution was favorable in 12 cases, marked by death in 1case and neurological sequelaein 2 cases.

Conclusion: ADEM is a rare pathology. There is no specific marker for the disease and cerebral magnetic resonance imaging is essential for diagnosis. Its management is based on high-dose corticosteroid therapy, which allows a cure in the majority of cases.

P36

STURGE-WEBER SYNDROME: CLINICAL SPECTRUM, DISEASE COURSE, AND OUTCOME OF 4 PATIENTS

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Background: Sturge-Weber syndrome is a congenital vascular disorder characterized by facial capillary malformation (port-wine stain) associated with venous and capillary malformations in the brain and eye. Neurological symptoms and alterations in other locations may also be observed.

Objectives: This study describes the clinical and epidemiological characteristics and different treatments in four patients diagnosed with Sturge-Weber syndrome in a tertiary hospital.

Methods : This retrospective study was conducted by reviewing the medical records of patients diagnosed with Sturge-Weber syndrome between 2014 and 2017.

Results: The first epileptic seizure occurred at the neonatal age for one patient and between the age of 6 months and 1 year for the other cases. All patients had seizures, which were well controlled in 3 cases by one antiepileptic (AE) treatment (1 case) and two AE treatment (2 cases). The psychomotor development was delayed in 2 patients and the two other had language disorders. Lepto-meningeal angioma is present in all the cases. Ophthalmologic examination was normal in 3 cases and showedipsilateralchoroidalangioma in 1 case.

Conclusion: There are multiple clinical manifestations of Sturge-Weber syndrome. Being familiar with all of them is vitally important for diagnosing and for monitoring and treating the condition correctly, which will improve the quality of life of these patients.

P37

ATTENTION-DEFICIT DISORDER IN NEUROFIBROMATOSIS TYPE 1: IS THERE DIFFERENCES WITH PRIMARY ADHD?

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Objectifs: Neurofibromatosis type 1 (NF1) is a genetic pathology predisposing to the development of tumors. The NF1 gene belongs to tumor suppressor genes and codes for neurofibromin, a protein playing a role in brain plasticity, memory and learning. Many children with NF1 have attentional difficulties and 30 to 50% present criteria for Attention Deficit Hyperactivity Disorder (ADHD). In previous works focusing on attention in NF1, few of them took into account ADHD criteria and none of them compared children with NF1 versus ADHD. The present study aims to compare (i) attentional profiles between children with NF1 with or without ADHD criteria, and (ii) compare how these profiles converged or diverged with those of children with ADHD.

Contenu: 33 children with NF1 strictly matched for age, sex and WISC-IV with 33 children with ADHD were included. Among children with NF1, 19 children met the ADHD criteria (NF1+adhd); 14 children had no ADHD criteria (NF1-). Children had realized computerized tasks: go/nogo (inhibition), continuous performance (sustained attention) and attentional capture (visuomotor coordination). All tasks parameters collected for participant were normalized for age and sex.

No significant statistical difference (ns diff.) between 3 groups was found for age, sex and the 4 scales of WISC-IV. Statistical analyses after FDR correction for multiple comparisons ($k=36$, p and $\alpha<.05$) showed: (i) more omissions for go/nogo in NF1+adhd than in NF1- and ADHD (ns diff. for response time (RT) and errors between 3 groups); (ii) more omissions, longer and more variable RT for CPT in NF1+adhd and ADHD than in NF1- (ns diff. for errors between 3 groups); (iii) more omissions, errors, longer and more variable RT for the capture in NF1+adhd and ADHD than in NF1- (compare with other tasks, worst scores were found for RT in the visuomotor coordination task for all groups, including NF1-).

Conclusion: Children of the NF1- group are impaired for the visuomotor coordination task –a slowness notably– but had normal scores in sustained attention. Children with a NF1+adhd criteria are impaired for all tasks (inhibition, sustained attention and visuomotor coordination). Attentional profiles were quite similar in NF1+adhd ADHD groups. This profile –omissions and great variability in various tasks– is characteristic to abnormal attentional fluctuations robustly evidenced in many previous ADHD studies.

P38

FAHR SYNDROME: STUDY OF 4 CASES

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Objectifs: Fahr's syndrome is a neuropsychiatric syndrome characterized by symmetrical and bilateral intracerebral calcifications located in the basal ganglia and usually associated with a phosphorus and calcium metabolism disorder. Clinical manifestations of Fahr's syndrome vary; it may start at different ages and have a variety of presentations.

Objective : To study the clinical, biological, radiological, therapeutic and progressive features of Fahr's syndrome.

Methods : A retrospective study of 4 cases of Fahr syndrome collected in our department during a period of 5 years (2018-2014).

Results: We report four cases of this syndrome, two were revealed by psychotic and cognitive disorders between the age of 9 and 13 years and the two others by epilepsy. In all cases, brain imaging and biology resulted in the diagnosis of Fahr's syndrome. Our patients were examined in regular follow-ups and all of them had no progression of symptomatology since the beginning of disease.

Conclusions: Fahr syndrome is rare. Clinical manifestations are varied and occur at any age without overrepresented ages of onset. Brain imaging shows calcifications of the basal ganglia.

P39

GLUTARIC ACIDURIA TYPE 1 ABOUT 2 CASES

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Background: Glutaric aciduria type 1 (GA1)is a rare neurometabolic disease with high morbidity.

Objective: To describe the MR imaging abnormalities in glutaric aciduria type 1 and to identify any association between the clinical and imaging features.

Methods: A retrospective study of 2 cases of GA1 collected in the paediatrics department of Hedi Chaker University Hospital. The diagnosis was made by chromatography of plasma and urinary organic acids.

Results: In the first case, it was a one-year-old male infant admitted for partial epileptic seizure with a right eye deviation with right upper extremities. He had no antecedent. On examination he had axial hypotonia, peripheral hypertonia, strong osteo tendinous reflexes and a bilateral Babinski sign. On MRI, he had signal anomalies of the periventricular white matter and bilateral basal ganglia and thalami. The second patient was a one-year-old male admitted for axial hypotonia. On examination, the patient had a macrophae at 48 cm (> 3SD), peripheral hypertonia, hypo reactivity, sharp osteo tendinous reflexes, epileptoid trepidation, and hepatomegaly. Cerebral computed tomography was normal whereas on MRI he had bilateral and symmetrical signal abnormality of the basal ganglia associated with cerebral cortical atrophy. The electroencephalogram showed a focus of biphasic spikes predominating at the right temporal level with occipital diffusion. The child was put on baclofen®, rivotril®, motor physiotherapy and hypoproteic diet. After a follow up of 4 years, the child has a psychomotor retardation and generalized hypertonia.

Conclusions: GA1is a rare organic aciduria. The patients present mainly spasticity. The diagnosis must be made early to begin the management and limit the sequelae.

P40

HEADACHE AND GILLES DE LA TOURETTE SINDROME: A COMPARISON BETWEEN PAEDIATRIC AND ADULT PATIENTS

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Objectifs: Only few studies analyzed the occurrence of headache in patients with Gilles de la Tourette syndrome (GTS) [1,2,3]. The aim of this study is to compare the prevalence and characteristics of headache in pediatric and adult patients with GTS and the relationship of headache with tic severity, psychiatric comorbidities and quality of life.

Materials and Methods: 109 children and adolescents with GTS (age range 6-17 years) were screened for the occurrence of headache between April and December 2014. Sixteen GTS patients (25%) showed headache and were compared with eighteen randomly selected GTS patients without headache with reference to tics' severity, psychiatric comorbidities (OCD, ADHD, anxiety, depression) and quality of life, using specific rating scales and questionnaires. 31 adults GTS patients, randomly recruited from a group of 200 patients, were screened for the presence of headache and underwent the same clinical assessment.

Results: Adults with GTS, compared with children and adolescents, show a higher prevalence of headache (48.4% vs 23%, $p<0.05$), higher tic severity, lower quality of life and higher prevalence of associated comorbidities: OCD (77,4% vs 52,9 %), anxiety (77,4% vs 32,4 %), depression (64,5% vs 26,5%). Children and adolescent GTS patients with headache show a lower severity and frequency of tics compared with GTS patients without headache.

Conclusion: Adult patients with GTS show a higher prevalence of headache and a more severe clinical phenotype compared to younger patients. Among children and adolescents, those with headache show a lower severity and frequency of tics, thus supporting the hypothesis that in young GTS patients, headache and tics could be considered different phenotypic expressions of a common etiopathogenetic mechanism (e.g. psychosomatic symptoms of poor anger and aggression management) [4,5].

P41

SUPER-REFRACTORY STATUS EPILEPTICUS IN PATIENT WITH SUBACUTE MEASLES ENCEPHALITIS AND HYPOGAMMAGLOBULINAEMIA

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Background: Subacute measles encephalitis (SME) is a rare complication in immunocompromised hosts and rarely immunocompetent hosts. Symptoms and signs can be general or multifocal, including mental changes, altered consciousness, loss of vision, myoclonia, or epilepsia partialis continua. Our aim is to describe a case of Super-refractory Status epilepticus in an immunocompromised patient with SME.

Results: Her medical history was remarkable for thrombocytopenia (11 years, treated with corticosteroid, infusion ev of Ig and Rituximab), two hospitalizations for pleuropneumonia (January and August 2017, 14 years), widespread macular rash, cough (June 2017), polyarthralgias and hypogammaglobulinaemia (September 2017, treated with monthly infusion ev of Ig). On December 2017, she presented headache and decrease of visual acuity with evolution toward blindness. From the 24th of December, daily myoclonic seizures of the face occurred, followed by sub continuous focal seizures, evolving in super-refractory status epilepticus not responsive to standard treatments and deep sedation. After a month we observed a progressive regression of the status epilepticus, despite that, the patient's neurological status continued to deteriorate, and she died after ten months.

Bacterial, fungal and viral cultures and antibodies were negative, metabolic and immunological screening were unremarkable. Cerebrospinal fluid, withdrawn on day 8 and day 14 from hospitalization, revealed only protein increase (47 and 60 mg/dL). The EEG showed slow-waves (SW) localized on the right hemisphere and continuous rhythmic SWs on the right regions, with controlateral diffusion; paroxysmal discharges were progressively followed by delta brushes pattern predominant on the right side and afterward by periodic burst of diffuse SW. MRI showed areas of abnormal intensity in the occipital lobes, with progressive extension to parietal-temporal, frontal and cerebellar regions. Studies on brain biopsy detected Measles and Parvovirus B19 RNA by RT-PCR.

Conclusions: Although measles immunization programs are present in Europe, several countries reported ongoing outbreaks since 2006–2007. In particular, between August 2017 and July 2018, 28 EU/EEA countries reported 14,118 cases of measles. As reported in Literature, our case confirms that immunocompromised patients may have more atypical presentations (antibodies undetectable, negative PCR on liquor) and complete vaccination schedule. Finally, we emphasize the importance of supporting herd immunity to protect immunocompromised patients.

C1

INFLUENCE SUR LE NEURODEVELOPPEMENT DE L'EXPOSITION AUX MÉTAUX DANS LA RÉGION DE BRESCIA ET TARANTO, ITALIE. / NEURODEVELOPMENTAL IMPACTS OF ENVIRONMENTAL EXPOSURE TO METALS IN THE AREAS OF BRESCIA AND TARANTO, ITALY

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Industrial emission of neurotoxic metals including manganese and lead, have been generated from ferroalloy and steel operations in the provinces of Brescia and Taranto, located respectively in the North and South of Italy. In the past, the exposure levels exceeded the current occupational and environmental health protective standards and have progressively decreased thanks to preventive intervention. Nevertheless, exposure related health impacts have been observed among occupationally exposed workers, showing dose-related dysfunction of motor coordination and cognitive impairment. A high prevalence of Parkinsonism was also observed in the province of Brescia, clustering in the vicinities of ferromanganese plants.

These observations prompted studies on children and elderly residing in these areas and showed effects on motor coordination, odor identification among children and elderly, and impacts on cognitive/executive functions (including visuospatial learning and memory), and behavior among the children. These various associations have been found in relation to a variety of exposure metrics: i) measurements of metals in environmental media such as soil, deposited dust indoor and outdoor, airborne PM10 and PM2.5 particles measured with stationary and personal sampling; ii) exposure biomarkers including blood, urine, hair, nails, saliva and shed teeth; iii) the distance between each individual participants' home address and the exposure point sources. Innovative techniques included the analysis of metals in shed deciduous teeth, which shows pre and postnatal exposure levels during these highly vulnerable life stages. In facts, early life exposure resulted associated to later cognitive and behavioral outcomes during childhood and adolescence. Gender differences were also observed with girls being more susceptible to exposure-related motor and cognitive effects.

Genetic predisposition was shown to influence both the internal exposure levels to manganese and the exposure related cognitive and behavioral outcomes. The genes considered in our studies are the SLC30A10 and SLC39A8. These two genes regulate the transport of manganese, which is an essential element, and have been recently discovered as responsible of a rare genetic disease causing hyper-manganesemia, Parkinsonism and liver disease in children with homozygous mutations. The non-homozygous mutations are more frequent and can influence both the internal exposure levels and, consequently, the neurodevelopmental outcomes in children with environmental exposure.

A pilot study using functional MRI explored differences of brain activities and showed that exposed children exhibit a reduction of activation signal, subjective odor sensitivity, olfactory bulb volume, and response of the limbic system, which regulates emotional responses. These preliminary finding prompted a new imaging and neuropsychological assessment of the cohort in Brescia, which is now formed of 720 subject entering adolescence. Therefore, this ongoing follow-up is focused on behavioral aspects.

The most recent analyses from our cohorts are considering the exposure to several metals with a 'mixed exposure' approach, using novel statistical models to manage complex multifactorial analyses. Socio-economic factors were also found to influence the exposure-related outcomes on cognition, especially in the poorer areas in Southern Italy, where in addition to cognitive impairment, alteration of the glucose metabolism were prominent at closer distance from the exposure point sources.

References available at https://www.ncbi.nlm.nih.gov/myncbi/collections/57169523/

C2

NUTRITION ET LE CERVEAU EN DÉVELOPPEMENT / NUTRITION AND THE DEVELOPING BRAIN

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The first 1000 days of life corresponds to a period of massive synaptogenesis, brain growth and development. Much of the brain's structure and capacity is shaped early in life. The brain's growth and developmental trajectory is not homogeneous and varies across time. For example, myelination increases abruptly at 32 weeks gestation and is most rapid through the first 2 years of life. There are also "critical" or "sensitive" periods during brain development during which there is particular vulnerability to environmental conditions, e.g. toxic stress and inflammation, social stimulation and nutrition. Conditions such as severe prematurity and cerebral white matter injury affect brain growth and specific structural brain development with subsequent functional consequences at both birth, infancy, early childhood and adolescence. Children who are brain injured during early childhood, however, often show substantial functional recovery due to brain plasticity. Animal studies have shown that following periods of nutritional deprivation functional brain recovery is only possible if nutritional correction occurs within a critical period. Adequate nutrition, both at macronutrient and micronutrient level is essential for the progression of normal brain development. It is remarkable that eradication of the world's three most common nutritional deficiencies - iron, zinc and iodine would increase the world IQ by 10 points. Providing an appropriate supply of long chain polyunsaturated fatty acids is important throughout infancy as fatty acids continue to accumulate rapidly in the brain grey matter through at least the first 2 years of life. Docosahexaenoic acid (DHA) is the most abundant omega 3 fatty acid in the mammalian central nervous system, and is specifically concentrated in membrane lipids of brain grey matter and retina. DHA participates in developmental processes of neurogenesis, neurite outgrowth, synaptic plasticity, axonal elimination and gene expression. DHA is produced from its precursor alpha linolenic acid by a series of enzymatic reactions. This conversion is, however, inefficient in humans and the majority of DHA must be obtained from the diet.A large multi-centre double blinded randomised control trial of DHA supplementation of breast feeding mothers or formula milk in preterm infants demonstrated higher Bayley MDI scores in preterm girls fed the high DHA diet compared to those fed the standard DHA diet (Makrides, et al. 2009). Other studies have concluded that LCPUFA supplementation "does not have a clinically meaningful effect on neurodevelopment as assessed by Bayley scores at 18 months" (Beyerlein, et al. 2010). Much previous work in this area has been confounded by usage of small doses of DHA for relatively short periods of time.A systematic review recommended that further work is needed to determine the extent of benefit of LCPUFA-supplemented formula on the mental development of preterm infant (Smithers, 2008). Our group in Oxford has been extending this work by investigating the prevention of neurodisability in children with and at risk of cerebral palsy. We applied a combination of DHA (given daily in maximum dosage over a period of 2 years) together with choline and uridine all molecules essential to the formation of brain phospholipids. The results of these studies will be presented (Andrew et al 2015; 2018a; 2018b).

C3

NEONATAL NEUROMETABOLIC DISEASES OUTCOME

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Inherited neurometabolic diseases are especially relevant in the neonatal period due to the high morbidity and mortality, the high risk of recurrence in affected families, the possibility of a new therapeutic options and the potential identification of asymptomatic infants through the neonatal screening (NBS) programs. These interventions aimed at early detection of asymptomatic children affected by certain neurometabolic diseases, with the objective to establish a definitive diagnosis and apply the proper treatment to prevent further complications, specially neurological sequelae and ensure a better quality of life.The scope of newborn screening (NBS) programs is continuously expanding. NBS programs are secondary prevention interventions widely recognized around the world. One of the most significant event in the history of neurometabolic diseases and neonatal screening was the discovery of phenylketonuria (PKU) in 1934. This disease has been the paradigm of inherited metabolic disease. It was also the first time that a biochemical explanation for the mental retardation was given. In addition, he developed a test for detecting the disease by adding ferric chloride to urine in two affected brothers, as a result of the reduction of iron, the urine turned green. He later showed it was due to accumulation of phenylpyruvic acid. In 1953 Bickel established an effective treatment for PKU. He proposed that the general development of children with PKU would be practically normal if phenylalanine would be restricted in the diet from the neonatal period. This fact led to the prospective studies of disease detection in many countries, and in 1958 the first population screening program was carried out in the city of Cardiff using the Folling test. The PKU panorama has changed for the future. The next paradigm was the introduction of tandem mass spectrometry in the NBS programs that makes possible the simultaneous measurement of several metabolites and consequently, the detection of several neurometabolic diseases in one blood spot and in an unique analysis.The role and scope of NBS is expanding. While traditional newborn screening was only concerned with few diseases associated with mental retardation, the programs now include disorders that can cause premature death, inherited neurometabolic diseases including lysosomal storage disorders, and others. It should be taken into account that any consideration to expand a NBS panel should involve a rigorous process of decision-making that balances benefits against the risks of harm. We aim to review the current situation of neonatal screening in worldwide, the changing outcome in the diagnosis of some neonatal neurometabolic diseases and demonstrate the scientific evidence of the benefits with the early and prompt therapeutical options in these diseases. We will also discuss future challenges. It should be taken into account that any consideration to expand a NBS panel should involve a rigorous process of decision-making that balances benefits against the risks of harm. However, despite all the advances with NBS techniques, not all neurometabolic diseases subjected to screening have a definitive treatment option. In some of them, early therapy allows to simply modify the course of the disease. We must not forget also that there are more than 1000 metabolic diseases and that many of them can present in the neonatal period, in addition there are no diagnostic methods of screening and therapeutic options, although the advances are still very limited. It is important for the pediatric neurologist to know these diseases, the rapid evolution of neonatal screening for neurometabolic diseases, the interest of their early recognition in the neonatal period and also to explore new therapeutic options to avoid serious neurological sequelae.

Rendez-vous à Lausanne

du 26 au 28 mars 2020