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SENP Scientific Committee

SUBJECT: EACCME accreditation granted EACCME-13825-G

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Venue: Lugano, Switzerland (19.–21.05.2016)
Event code: 13825

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Brussels, 15. 4. 2016 The UEMS – EACCME Secretariat

Résumés du congrès
Abstracts

01

ECHOLALIC FUNCTION IN THE COMMUNICATIVE DEVELOPMENT OF AUTISTIC CHILD: FROM THEORETICAL BASIS TO CLINICAL EXPERIENCE

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Autistic echolalia is traditionally considered an authomatic behavior without communicative function. Literature usually separates echolalia into immediate and delayed echolalia. Another type, called mitigated echolalia, is represented by echolalic productions modified from the child through own linguistic elements. This study aims to examine echolalia in autism through a qualitative analysis of echolalic utterances, in order to interpret their possible meanings and to correlate echolalia to communicative development of the child.

METHOD
We analyzed the speech of three autistic children (S1: 5y 7m, S2: 8y 6m, S3: 10y) through logopedic assessment of linguistic abilities and audio-recordings of verbal production. The recorded data have been divided into spontaneous and echolalic utterances: echos have been distinguished in immediate, delayed or mitigated echolalia. Then, we attributed a function to each immediate and delayed repetition on the basis of Prizant-Dunchan (1981) and Prizant-Rydell (1984) classifications.

RESULTS
Linguistic abilities: S1: delayed understanding abilities and very poor production characterized by vocalizations, sporadic simple incomplete sentences and echolalia; S2: delayed understanding abilities and better expressive language than in S1; S3: delayed understanding abilities and well-structured expressive language.
Percentage of echolalia on total production: S1: 64% (47% immediate, 48% delayed, 5% mitigated); S2: 22% (44% immediate, 33% delayed, 23% mitigated); S3: 30% (32% immediate, 48% delayed, 21% mitigated).
Echolalic functions: immediate echolalia: greater use of affirmative, turn-taking and declarative functions; delayed echolalia: a more etherogeneous framework: S1 uses mainly verbal completion, while S2 and S3 use more varied functions; we didn't find functions for mitigated echolalia because we consider it a real expression of a communicative intent.

DISCUSSION
These results show how echolalia could be considered a linguistic strategy with precise communicative aims, not only but it emerges that echolalic productions correlate with level of linguistic competences.
The percentage of echolalia and its distribution, indeed, vary with linguistic development: the percentage of echolalia is greater in S1, where linguistic abilities are poorer and the number of functions, specially about delayed echolalia, seems increasing in S2 and S3, that show better language abilities. It is noteworthy that mitigated echolalia is represented almost exclusively in S2 and S3.
Consequently, we could think about an evolutive pattern in which the passage from echolalic to spontaneous language is mediated by mitigated echolalia: in fact, S1 presents much of echolalia, but mitigations are minimal compared to S2 and S3.
Anyway, a deeper understanding of echolalia in communicative development of autistic child is recommended.

EARLEY DIAGNOSIS OF AUTISM SPECTRUM DISORDERS WITH THE USE OF THE M-CHAT: EXPERIENCE IN THE SOUTHERN PART OF SWITZERLAND

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INTRODUCTION: Although early diagnosis and treatment of children with Autism Spectrum Disorders (ASD) are considered crucial for improving the level of functioning and quality of life, ASD is not always accurately diagnosed during the preschool years. In fact, previous studies show that ASD is often not recognized until entry into public school, especially for higher functioning individuals. For these reasons, we introduced the Modified Autism Checklist for Toddlers
(M-CHAT) during the annual check-up for 2-year-olds. The aim of this study was to determine the impact of this procedure in the precocity of ASD diagnosis in the southern part of Switzerland.

METHODS: In 2009 we introduced the screening instrument M-CHAT at the annual check-up for 2-year-olds. The M-CHAT is an autism questionnaire for parents consisting of 23 questions about early developmental issues with particular regard to social interaction. Children who were suspected of having ASD were referred to the Paediatric Neurology Unit in Bellinzona, for specific assessment.

RESULTS: The paediatricians were instructed to use the M-CHAT questionnaire during the annual check-up for 2-year-olds. During the first four years (2009-2012) 41 children (33 M, 8 F) were evaluated and diagnosed with autistic spectrum disorder was made; the mean age of the diagnosis was 3.3 years. In the last 3 years (2013-2015), the same screening method allowed the diagnosis of autism in 36 children
(29 M and 7 F). The mean age for ADS diagnosis was 2.5 years.

CONCLUSION: After the introduction of the M-CHAT during the annual check-up for 2-year-olds, we observed an increased number of children that underwent assessment for suspicion of ASD in our department comparing the previous years. Importantly in the last few years, the mean age of diagnosis was 2.5 years, showing a progressive benefit of the currently screening method. This approach shows the importance of paediatricians in the early detection of ASD. Paediatricians should already begin to recognize children with ASD at the preschool age in order to begin therapy as soon as possible. Early diagnosis and intervention may have a decisive impact on a child's development and subsequently on integration into kindergarten and public schools.

03

ASSESSMENT OF AUTISTIC-LIKE SYMPTOMS IN CHILDREN WITH SEVERE CONGENITAL VISUAL IMPAIRMENT: A PILOT STUDY

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Study objectives: a delayed symbolic play, difficulty in social interaction with peers, echolalic speech and increased stereotyped behaviors are commonly observed in visually impaired (VI) children.
These behaviours resemble those of children with ASDs, and coupled with the fact that the most common methods used to score autistic behaviours still include several items linked to vision, may contribute to an overrepresentation of ASDs within VI children. This study aimed to evaluate the occurrence of autistic-like symptoms in VI children, in order to determine if autism can be reliably diagnosed in VI children and to identify if specific symptoms could have a greater specificity that may be useful in the diagnostic evaluations.

Methods: the sample comprised 20 children: 10 children (4 F, mean age 4y 7m) with severe congenital VI and 10 autistic sighted children, matched for sex and age to the subjects with VI. A video-recorded behavioural observation, the CASD, the standard and the modified version of ADOS-2 were used to assess autistic symptoms in all the patients. ADOS-2 was sistematically modified excluding items specific to visual responsiveness and introducing alternative tasks based on tactile or auditory experience. Results: according to the results of the modified ADOS-2 only 3 children were classified in the category of autism, 3 in the category of autism-spectrum while 4 were classified in the non-spectrum category. Considering the items of the modified ADOS-2 singly, we found that some symptoms (e.g. related to Eye Contact) seem to be most reliable in discriminating autism from behaviours common to most children with congenital VI, while other behaviours (e.g. related to Pointing) seem to have poor specificity.
In contrast to autistic sighted children, children with VI showed results within the normal range in the 'problems with social interaction' and in the 'problems with attention and safety'CASD domains. Comparisons of current behaviour with parent-reported behaviours from a younger age suggested that some symptoms in VI children may improve with age.

Conclusions: the routine screening of ASDs for children with congenital VI is mandatory, and this study has provided the preliminary evidence that modified autism diagnostic measures are useful in conducting the diagnostic evaluations. Clinicians should be cautious of diagnosing ASDs in VI children, since it appears that some behaviours might reflect the influence of the visual deficit on early interactive experiences and that some symptoms may improve over the course of development.

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Study objectives: the aim is to analyse the earliest and most specific signs and symptoms of autism spectrum disorder (ASD) for early diagnosis. We present a retrospective study of a cohort of toddler/children showing risk symptoms for ASD.

Methods: the sample consisted of 50 subjects (35 M), aged between 26 and 62 months (mean 36 months; 11 aged <30 months) referred to the Autism clinic of Child Neuropsychiatry Unit of Brescia in a period of 18 months. Each subject underwent to the following protocol: detailed medical history, Checklist for Autism Spectrum Disorder-CASD, neurological examination, playing observations, cognitive evaluation; if the clinical suspect was confirm, we administered ADOS-2. Children with autism and / or psychomotor delay also carried out a sleep EEG, Karyotype, FRAXA and Array CGH.

Results: in 32/50 (64%) subjects were confirmed the diagnosis of ASD, in 13 subjects other diseases were diagnosed. 5 assessments are under way. Comparing the 32 patients with ASD diagnosis with the 13 non-autistic patients we found some differences in mean age (32 vs 44,4 months) and nationality (34% vs 47% foreign). Analysing CASD profile we found quantitative differences: the mean total score of autistic children is higher than non autistic children (16,6 vs 9,8, cut off 15). In non autistic sample globally all symptoms are present, but less represented: 5 patients obtain a total score compatible with risk of autism and 5 a total score compatible with ASD; during the play observation these symptoms in the non-autistic sample appear more flexible than in autistic children. In the DSA sample we divided children (> 31 months) from toddler (< 31 months), basing on ADOS criteria. Considering ADOS-2 results, Toddler's profile is characterized specially by impairment of "Social and affection skills", while "Repetitive behaviours" are more represented in children. Marker of autism in both groups seem to be "Unusual eye contact", "Integration of vision", "Start and quality of social openings". Only one of the children younger than 31 months resulted not autistic.

Conclusions: our study shows that the autistic patients presents more symptoms and more severe impairment of social functioning. We confirms that impairment in social attention and social communication is potential early marker of ASD in toddlers; in children "repetitive behaviour and mannerisms" become significant markers too.

05

STRETING EFFECTS BY SQUATTING POSTURE FOR SUBCLINCAL SPASITIC TYPE CEREBRAL PALSY

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Introduction: It is not rare that the children who have developmental delay of language have also delay of motor function. But if motor dysfunction is very mild, it is sometimes overlooked as an ignorable phenomenon. Patients visit in our center mostly around the age of three years, and their main complaint is 'delay of speech' usually without apparent motor complaints. Experimentally, we know such a group has a risk of developmental disorders, and if they have mild motor symptoms, for example, easy to fall down, we have a tendency to suppose that it is due to coordination disorders and sensory integration therapy might be prepared for them, but for some cases, it is not effective. Among such patients, we found that there was a group who suffered from mild spastic symptoms and that it was easily curable by a stretching maneuver. We report here about this group.

Materials and Methods: The subjects were 7 patients from the age of 2 to 5 years, 2 males, 5 females, who visited in our center with a complaint of 'delay of speech'. They started to walk alone from the age of 10 to 20 months. After an interval of several months or years, their parents became anxious about that their children easily felt down and that this tendency did not show amelioration. By our neurological examination, we found they had common symptoms. 1) Normal posture at rest, 2) Appearance on walking of mild spastic posture of lower extremities 3) All of them had either hyper-reflexes of lower extremities or positive Babinski sign, and 2 cases had both of these symptoms. 4) They had abnormal peri- and neonatal histories. All of them were born by emergent caesarian section. 6 cases were born as a baby small for date. 3 cases were under mechanical ventilation in neonatal period. We practiced them a stretching maneuver by 'Squatting Posture' (an original reverse-posture for spastic palsy)

Results: Just after the practice of this maneuver, their spastic walking pattern immediately became milder. We advised their parents to continue this maneuver at home once a day. And they fell never easily down as before.

Conclusions: We found there is a group of subclinical spastic palsy.
This group shows late motor dysfunction, for example easy to fall down. As a way to cure this dysfunction, stretching maneuver by Squatting Posture is a simple and effective way. We must not overlook this group.

HIGH PREVALENCE OF PATHOLOGIC COPY NUMBER VARIATIONS DETECTED BY ARRAY COMPARATIVE GENOMIC HYBRIDIZATION IN CHILDREN WITH AUTISM SPECTRUM DISORDERS: THE EXPERIENCE OF SOUTHERN SWITZERLAND

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INTRODUCTION

Autism spectrum disorders (ASDs) are a heterogeneous group of disorders characterized by abnormal social/communication and restricted, stereotyped, activity/interests. While the vast majority of causes of ASDs is still unexplained, 2-20% of ASDs patients presents pathologic Copy Number Variations (CNVs) detected by array comparative genomic hybridization (array-CGH). We collected data from
21 children presenting ASDs. Array CGH detected pathologic CNVs in
6/21 (29%). Our results strongly suggest the application of array CGH as first tier genetic investigation in patients with ASDs.

MATERIALS AND METHODS

Data of children referred to our institution because of ASDs were prospectively collected over 2 years. They included sex, age at first evaluation, results of Autism Diagnostic Observation Schedule and Autism Diagnostic interview (ADOS/ADI), metabolic screening, serologic screening for celiac disease and thyroid function, EEG, brain MRI and array-CGH testing.

RESULTS

Between 1st January 2010 and 31st December 2011, 23 children with ASD were referred. None of them presented characteristic dysmorphic traits suggesting a specific genetic condition, so that all 21 patients underwent array-CGH studies. 6 out of 21 patients (29%) presented pathologic copy number variations. Thyroid function tests, celiac and metabolic screening as well as brain MRI were normal in all 6 children with pathologic array-CGH testing. EEG showed abnormal activity in 3 out of 6 patients (50%) with pathologic array-CGH results, while only
2/14 (14%) children without pathologic array-CGH presented abnormalities at EEG (3 children with normal array-CGH results did not undergo EEG-testing). While comparing patients with and without pathologic array-CGH results, no significant difference was identified in ADOS and ADI scales.

CONCLUSION

In this study, pathologic copy number variations were detected in 29% of children with ASDs undergoing array-CGH analysis. This approach might represent a first tier investigation tool in children with autism spectrum disorders of otherwise unexplained etiology.
Noteworthy, in the present case series, most of the investigations performed in children with ASDs (brain MRI, metabolic, celiac and thyroid function screening, ADOS/ADI scales) failed to predict pathologic results at array-CGH analysis.

DEVELOPPEMENT DU MUSCLE CHEZ LE FOETUS HUMAIN

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BUT : Le développement des techniques de diagnostic prénatal permet de dépister de plus en plus tôt les foetus porteurs d'un trouble de la mobilité périphérique. A l'instart des explorations menées chez l'enfant, l'exploration anténatale d'un trouble de la motricité comporte le recherche d'une cause centrale (cerveau et moelle) ou périphérique (muscle, jonction neuro-musculaire, nerf
périphérique) avec des outils beaucoup plus limités où la morphologie occupe une place majeure. Dans ce cadre, l'analyse de la biopsie musculaire est primordiale.

METHODOLOGIE : Nous présentons ici les divers stades évolutifs de la morphologie musculaire (quadriceps) obtenue après biopsie post-mortem durant toute la grossesse, avec analyse optique et ultrastructurale.

RESULTATS : durant le premier trimestre, les myocytes post-mitotiques se sont assembles pour constituer les myotubes primitfs, a noyau central, rapport nucléoplasmatique élévé; le muscle primordial a un aspect homogène , avec des cellules musculaires globalement de même calibre, les myofibrilles sont présentes dans le cytoplasme avec une striation discernable; entre 15 et 20 semaines, apparaissent les myotubes secondaires sous la forme d'une deuxième population de cellules musculaires, de plus petite taille, exprimant la myosine rapide,alors que le myotubes primaires, volumineux, expriment la myosine lente. Les noyaux sont encore centraux , mais seront progressivement déjettés en périphérie; après 22 Sa, il ne persiste pas de noyau périphérique; les myotubes secondaires vont se multiplier, jusqu'à devenir la population majoritaire et croître, effaçant progressivement l'anisocytose du muscle. Parralèlement, les cellules musculaires expriment la vimentine et vont en s'enrichissant en desmine; la mérosine révèle un membrane basale qui englobe initialement myotube primaire et secondaire, puis individuellement chacun des myocytes (autour de 20SA). Durant le 3ème trimestre, toutes les cellules musculaires sont de même calibre, les myocytes de type 2 sont majoritaires et la vimentine commence à décroitre jusqu'à sa disparition à la naissance. le rapport nucléoplasmique a diminué avec l'augmentation du calibre des fibres.

CONCLUSION : l'analyse morphologique du muscle foetal est donc non seulement possible mais également riche d'enseignement diagnostique.
dans notre expérience, nous avons ainsi pu envisager pour des foetus avec des troubles de la mobilité des diagnostic de myopathie congénitale ou d'atteinte neurogène.

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Depuis les recommandations de l'EACD en 2012, le diagnostic de TAC (Trouble d'Acquisition de la Coordination) repose sur les critères diagnostiques du DSM et un score pathologique au M-ABC retenu comme le « gold standard » test. Nous présentons ici le cas d'un enfant répondant aux critères diagnostiques du DSM-V mais dont les scores au M- ABC n'étaient pas pathologiques alors que ceux obtenus au test PVSE (test des Perceptions Visuo-Spatiales Elémentaires) l'étaient.
Ce cas clinique nous amène à poser les questions suivantes : un trouble praxique visuo-spatial et non gestuel relève -t- il d'un TAC ? Quelle place complémentaire pour le test PVSE à côté du M-ABC ?
Présentation du cas clinique : il s'agit d'un garçon adressé à l'âge de 9 ans pour un avis diagnostique en raison de difficultés à l'écrit intéressant le graphisme, la lecture et l'orthographe.
Lors de l'entretien, l'enfant était décrit comme maladroit dans les activités de la vie quotidienne. Un premier bilan psychométrique à l'aide de la WISC-IV révélait des scores en dessous de l'intervalle de normalité pour les épreuves cubes et codes. Le bilan attentionnel et exécutif à l'aide de la TEA-Ch montrait des perturbations de l'attention auditive et visuelle avec préservation des fonctions exécutives. Le score obtenu au QTAC confirmait la maladresse. La note totale de dégradation au M-ABC était supérieure au 15eme centile alors que le score global au test PVSE était inférieur au premier quartile, le score le plus bas étant obtenu au test de discrimination de points en lien avec l'attention visuo-spatiale. Au BHK, la qualité de l'écriture était très déficitaire et la vitesse d'écriture à la limite inférieure de la moyenne.

Discussion- conclusion : ce cas clinique pose la question du cadre nosographique en cas de trouble praxique visuo-spatial sans trouble praxique gestuel et de la place complémentaire du test PVSE à côté du M-ABC dans l'évaluation des troubles visuo-spatiaux élémentaires dans le TAC.

OPTIC NEURITIS IN CHILDREN : PROGNOSTIC FACTORS AND EVOLUTION. A RETROSPECTIVE STUDY ABOUT 28 CASES

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INTRODUCTION : Optic neuritis (ON) in children can be the first presentation of multiple sclerosis (MS). Brain and medullary magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis allow for an early identification of high-risk patients. The purpose of this study was to determine visual evoked potentials (VEP) characteristics during a first ON event in children and their prognostic value concerning MS.

METHODS : All patients younger than 18 years old addressed at our hospital for a first ON event from 1999 to 2014 were included.
Systemic, metabolic and genetic diseases were excluded.

RESULTS : We included 28 patients, with a mean follow-up of 4,3 ± 3,2 years. Five patients (18 %) were diagnosed with MS. VEP were performed in all patients. Median P100 latency was higher in MS group than in non-MS group (136 ms versus 116 ms ; p _ 0,05). The risk of being diagnosed with MS was higher if P100 latency was superior to 125 ms (RR 1,8 ; CI [1,003-3,2] ; p _ 0,05).

DISCUSSION : VEP are a new prognostic factor of evolution to MS, during a first ON event in children. Because of their reproductibility and non-invasive nature, VEP should be systematically performed in association with brain and medullary MRI and CSF analysis, during all first ON event in children.

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WDR81 is a gene involved in CAMRQ2 (congenital ataxia with mental retardation and disequilibrium syndrome) reported by Gulsuner and al in 1995 in a consanguineous Turkey family. Patients arbored a global cerebellar atrophy at MRI and dysplayed homozygous missence mutations in WDR81. Since then, no other patients were described.
We report here 4 news patients with WDR81 mutations: the first patient -an offspring consanguineous Morrocan family- presents feature of CAMRQ2 but harbors a new homozygous missence mutation in WDR81 (phenotype A); the 3 latter patients are siblings – one child (patient 2) and two twins fetuses (patients 3 and 4) - harboring a composite heterozygous mutation in WDR81 but display a different and new phenotype such as microlissencephaly (phenotype B).
The aim of our study is to compare brain involvement and lesions evolution in these two phenotypes in order to study if some hallmark brain features can be related to WDR81 mutations whenever the clinical phenotype and genotype. We compiled MRI data (patient 1 at 4 and 17 years; patient 2 at 4 years) and neuropathological data (patients 3 and 4 at 32 GW).

Results: Comparing both phenotypes at 4 years, it appeared that phenotype A is defined by cerebellar atrophy with preserved supratentorial structures, while phenotype B is defined by a severe microcephaly with both supra and infratentorial involvement, hippocampal malrotation, and striatum and white matter abnormalites.
However, corpus callosum involvement was comparable in both phenotypes with a caudal underdevelopment. Comparing intraphenotype evolution (patient 1 at 4 years vs same patient at 17 years and fetus 3,4 vs patient 2) we observe that in both phenotypes telencephalic structures remain unchanged while cerebellar atrophy worsens with age.
Neuropathological study of the fetal cases reveals an extended and depopulated germinal zone as an abnormal cortical cytoarchitecture with neuronal depletion.

Conclusion: We report a new phenotype in WDR81 mutations as the evolutionary pattern of the brain lesions . We demonstrate that whenever the phenotype, WDR81 mutation give rise to common hallmark brain lesions. These data are in accord and complete the available data earlier reported (Cavallin and al, 2016). They provide original insights in the physiopathology of the brain lesions related to this mutation.

011 BLAKE'S POUCH CYST: ATYPICAL PRESENTATION IN AN OTHERWISE NORMAL DEVELOPED 18-MONTHS-OLD CHILD AND REVIEW OF THE LITARATURE

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Introduction:
Blake's pouch cyst (BPC) is a rare cystic malformation of the posterior fossa that is caused by lack of fenestration of the Blake pouch, resulting in absence of communication between the fourth ventricle and the subarachnoid space and leading to tetraventricular hydrocephalus. Children with BPC typically present with macrocephaly and hydrocephalus in the neonatal or infant age. Here we present an 18-month-old child with an atypical clinical presentation of BPC and reviewed the available literature.

Case report:
An 18-month-old girl presented with a rapidly progressive cerebellar ataxia over a few months leading to complete inability to walk after an initially age appropriate motor development. The neurological examination at 18 months of age revealed truncal and limb ataxia with intention tremor and dysdiadochokinesia. In addition, her head circumference was 52 cm (2.5 cm above the 97th percentile). A retrospective evaluation of the head circumference growth revealed a progressive increase since the age of 9-12 months. A brain MRI showed a marked tetraventricular hydrocephalus with an infravermian cyst, a normal size and shape of the cerebellar vermis, and an inferior displacement of the choroid plexus along the antero-superior aspect of the cyst. A ventriculo-peritoneal (VP) shunt was placed few days after the MRI. After a well-managed complication related to over drainage of the VP shunt, the child showed a marked recover of her motor functions and the head circumference showed a mild decrease on the last follow-up at the age of 30 months.

Discussion:
Our patient shows that BPC may present outside of the neonatal age or infancy with progressive ataxia. In older patients, hydrocephalus may be absent due to the normal function of the foramen of Luschka or be present, but decompensate later in life after an intercurrent event such as trauma or infection (postnatal secondary form). Because of the lack of intercurrent events and neonatal/infancy symptoms, it remained unclear whether our patient has a congenital or a postnatal secondary BPC. Neuroimaging allows to differentiate between BPC and other posterior fossa cystic malformations including Dandy-Walker malformation, arachnoid cysts, and mega cisterna magna. The differentiation between BPC and other posterior fossa cystic malformations is important in terms of management and prognosis of outcome.

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Mutations in CACNA1A, which encodes the transmembrane pore-forming subunit of a voltage-gated calcium channel, are associated with sporadic and familial hemiplegic migraine type 1 (SHM1, FMH1), familial episodic ataxia type 2 and spinocerebellar ataxia type 6. The clinical spectrum can be wide ranging from moderate to severe impairment and paroxysmal versus progressive course. Acetazolamide or calcium channel blockers may have a positive effect on migraine or episodes of ataxia.

Patients and methods : We present two patients with de novo CACNA1A alterations but a clinical picture of congenital, slowly progressive non episodic ataxia with stroke-like episodes.

Case1: 14 year-old girl with congenital ataxia, abnormal eye movements and developmental delay who presented severe attacks of hemiparesis, coma and seizures initially triggered by minor head traumas since the age of two years. These episodes were correlated to hemispheric swelling on brain MRI. Subsequent MRIs showed focal atrophy of both posterior temporal regions and progressive cerebellar atrophy.

Clinical worsening occurred under flunarizine, but at 9.5 years cessation of the attacks was achieved under acetazolamide treatment. A de novo heterozygous deletion of 3 bp (c.4503_4505delCTT

:p.Phe1502del) in exon 28 of CACNA1A was found leading to an amino-acid change in one of the critical transmembrane domains of the protein. Electrophysiologic in vitro studies demonstrated a gain-of function (García Segarra et al., J Neurol Sci, 2014).

Case 2: 14 year-old girl with a history of tremor and hypotonia during the first year of life. She presented three episodes of acute strokes involving successively both parieto-occipital and left frontal cortical areas after minor head trauma as well as spontaneous episodes of alternating hemiparesis. At follow up she presented ataxia, severe intellectual disability and cerebral visual impairment. Subsequent MRIs showed bilateral parieto-occipital atrophy and progressive cerebellar atrophy. Extensive work up led to rule out a metabolic disease, especially MELAS. Whole exom sequencing revealed a de novo missense mutation (c.2134A_G :p.ILe712Val) in CACNA1A. The characterization of this mutation is pending.

Conclusions: These two cases, sharing similar clinical findings, illustrate the wide clinical spectrum of CACNA1A related diseases. The combination of stroke like episodes, sometimes triggered by trivial head trauma, progressive cerebellar symptoms, which can be difficult to recognize during the first year of life, and cerebellar atrophy, are good clues to search for CACNA1A mutations. Given the therapeutic opportunities, early diagnosis may lead to a reduction of paroxysmal episodes and thus to a better quality of life.

013 ARRESTED HYDROCEPHALUS IN CHILDREN: FIVE CONSECUTIVE REPORTED CASES AND COMPREHENSIVE REVIEW OF THE LITERATURE AVAILABLE TO DATE

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Hydrocephalus is defined by an increase in size/volume of the ventricular system and may be progressive or arrest spontaneously. In arrested hydrocephalus (AH), the balance between production and absorption of the cerebrospinal fluid is restored. In this rare condition ventricular dilatation is stable, and the intracranial pressure returns to normal values.
Here we report on clinical and neuroimaging findings as well as long-term follow-up of five children with AH. In addition, we performed a comprehensive review of the available literature.
Patients with AH do not have symptoms of increased intracranial pressure and do not need neurosurgical intervention. An early and correct differentiation between progressive hydrocephalus and AH is crucial in terms of management and prognosis. The presence of enlarge extraaxial-spaces as well as perivascular spaces on brain MRI favors the diagnosis of AH.

CHILDHOOD ABSENCE EPILEPSY (CAE) AND EYELID MYOCLONIA WITH ABSENCES (EMA): OVERLAP CASES?

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Study objectives: CAE is an idiopathic generalized epilepsy characterized by very frequent typical absences. The ictal EEG findings are generalized spike-wave discharges at 3 Hz and the interictal EEG has a normal background activity. Hyperventilation and intermittent photic stimulation induce absence seizures in 83% and 21% of patients, respectively (Matricardi S, 2014). We aimed to report the clinical and electroencephalographic features of a cohort of children with CAE that evolve to EMA after antiepileptic drug withdrawal.

Methods: we reviewed the clinical data and EEG features of patients with CAE observed at our Center in the last ten years. We selected children with CAE diagnosis (according to Panayiotopoulos criteria,
2005) that evolve into EMA (characterized by eyelid myoclonus associated with brief absences, generalized paroxysmal activity induced by eye closure and photosensitivity, Vaudano AE, 2014) after therapy withdrawal.

Main results obtained: we identified seven patients (one boy and six
girls) affected by CAE. In two cases there was at least one first-degree relative affected by epilepsy. The mean age at seizure onset was 7.3 years (range: 5.5–8.11). All the patients presented typical absences associated to 3–4 Hz spike-wave discharges at video-EEG. Hyperventilation and intermittent photic stimulation induce seizures in 100% and in 14% of patients respectively. All the subjects except one presented a good response to valproic acid (mean age of seizure free: 4.2 months, range: 1–12). All the children stopped antiepileptic therapy within 3 years. After antiepileptic drug withdrawal all the seven subjects presented seizures characterized by eyelid myoclonus associated with brief absences, generalized paroxysmal activity precipitated by eye closure, and photosensitivity.
One case presented also a generalized tonic-clonic seizure during Intermittent Photic Stimulation – IPS (Christmas tree) and two showed up gaze deviation associated with impairment of consciousness and unresponsiveness. When wearing the Z1 lens, three children showed any abnormalities on their EEG when exposed to flashing light.

Conclusion: CAE generally has a good prognosis for remission of seizures and successful antiepileptic drug withdrawal. CAE patients may develop generalized tonic-clonic seizures (2014, Matricardi S) or a Juvenile Myoclonic Epilepsy (Camfield CS, 2014) in 8-69% and in 15% of cases respectively. Our study documented that children with CAE may also develop EMA. The possible evolution of CAE into EMA is an interesting observation that opens the discussion about EMA classification.

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015 ELECTRO-CLINICAL FEATURES OF VIDEO-EEG RECORDED SEIZURES IN 51 PATIENTS WITH TSC RELATED EPILEPSY

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Purpose: Tuberous sclerosis complex (TSC) is an autosomal dominant, multisystemic disease with variable expression. Epilepsy is the most common neurological symptom occurring in 80-90% of affected individuals, causing significant morbidity and mortality. Despite the large number of patients reported, the electro-clinical phenotype associated with TSC epilepsy is poorly described. We analyzed seizure semiology through ictal video–electroencephalography (V-EEG) recordings in a large series of patients.

Methods: 51 patients were comprised, with TSC related epilepsy, followed in 3 Tertiary Care Centers in Milan and analyzed clinical history and ictal V-EEG recordings.

Results: 51 patients (22F/ 29M) with a median age of onset of epilepsy 22.55 months (range: 1 day – 16 years). Epilepsy onset in the first year of life in 36/51 patients (70%), in 10 during the neonatal period. 33/51 patients experienced epileptic spasms in their life, with late-onset (>2 years) in 5. 37/51 patients showed daily seizure frequency at the time of evaluation.
We identified 4 different groups of patients: patients with focal epilepsy (18/51), with epileptic spasms and focal seizures (17/51), with persisting epileptic spasms only (2/51) and presenting with a Lennox-Gastaut evolution (14/51). Focal seizures were recorded in 42/51 patients, epileptic spasms in 9/51, tonic seizures in 4/51, atypical absences in 2/51, myoclonic seizures in 2/51, and atonic seizures in 1/51. In 10 patients we recorded polymorphic seizure types.

Conclusion: Focal seizures without generalization result as the most frequent seizure type recorded, with variable foci but predominant involvement of the fronto-temporal regions. Data obtained on seizure semiology analysis showed minimal motor signs in neonatal period. Epileptic spasms were frequently asymmetrical and manifestation had lateralizing features (eye deviation, asymmetric limb involvement, etc.), especially those with late onset.

SLEEP DISORDERS IN CHILDREN AND ADOLESCENTS WITH EPILEPSY: AN OBSERVATIONAL STUDY

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Study objectives

This research studies children and adolescents suffering from epilepsy, to assess the presence and prevalence of sleep disorders and to investigate the reciprocal interactions between epilepsy, sleep disorders and behavioral problems.

Methods

We enrolled 60 children (34 M, aged 3-17 years, mean BMI 19), suffering from epilepsy, diagnosed according to the ILAE classification of 2010, compared with a homogeneous group of healthy controls for age, sex and BMI. We used the SDSC (Sleep Disturbance Scale for Children) to assess the presence of sleep disorders and the CBCL (Child Behavior Checklist) to describe the behavior and to identify any psychopathological problems.

Main results obtained

Patients with epilepsy have obtained high scores both at SDSC ($p < 0.05$ at DIMS and DES, 13% and 20% vs 0% and 2% in controls) that the CBCL ($p < 0.05$ for almost all categories). 66.7% of patients with pathological SDSC presented seizures in sleep. Pathological scores at CBCL were related to the frequency of seizures (57% with daily seizures), the presence of seizures during sleep (42.8%), polytherapy (57.2%) and the presence of autistic spectrum disorders or intellectual disabilities (43%).

Conclusions : A pathological score at SDSC should always suggest to investigate the presence of seizures during sleep, through nocturnal laboratory polysomnography. A pathological score at CBCL should lead to reconsider anti-epileptic treatment and to look for the presence of sleep disorders. The treatment of children with epilepsy should consider a possible co-morbidity with a sleep disorder.

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017 AVANCEES DIAGNOSTIQUES DANS LES ATAXIES CONGENITALES ET TRES PRECOCES: INTERET DU SEQUENCAGE HAUT DEBIT CIBLE

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Congenital non-progressive ataxia (CNPA) are responsible for hypotonia in the first months followed by a non-progressive ataxia associated or not with intellectual deficiency. Many genes with various modes of inheritance are involved. For most of these genes the exact incidence of each is unknown. Among early-onset ataxia, some are progressive but may be difficult to distinguish from CNPA in the first years of the disease, particularly in some very slowly progressive forms.

Aim of the study: To assess the respective contribution of the CNPA known genes using new generation sequencing (NGS) and the associated phenotype.

Patients: 140 patients recruited from our reference center. Inclusion criteria: Non progressive cerebellar ataxia at the time of examination and neurological symptoms observed before age of 2 years. Exclusion criteria: Joubert syndrome; CDG; Chromosomal anomalies; Muscle weakness and elevated creatine phosphokinase (CPK); Clearly progressive ataxia.

Methods: Targeted NGS of 35 known genes. Design: As patients affected with very early progressive ataxia might have a slowly progressive course and might been misdiagnosed as CNPA, the design of our panel included 19 genes responsible for CNPA, 5 genes responsible for early-onset ataxia and 11 confidential candidate genes.

Results-conclusion: we identified causal mutation in 27 patients (19,3%). Interestingly, in 63%, the mutation occurred de novo. The genes ITPR1 and SPTBN2 were the most frequently involved genes. In conclusion, targeted NGS could allow the detection of causal mutations in 20% of CNPA patients. However, regarding the part of undiagnosed patients (80%), alternative strategies like "mini-exome" might be discussed.

AN UNRAVELLING COURSE OF DEVELOPMENTAL REGRESSION: WHERE TO START, WHEN TO STOP?

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Objectives:
Neurodegenerative diseases in children are rare. Various attempts have been made to classify them according to the mode of presentation, age of onset or spectrum of clinical findings. Reaching a specific diagnosis has therapeutic, prognostic and genetic counselling implications. Despite numerous practical approaches, a substantial proportion of clinical cases remain without a diagnosis. We seek to outline the ongoing medical work-up carried out in one of our patients, who first came to our hospital five years ago.

Method:
A Chinese 7 year-old boy was addressed to our neuropediatric unit for evaluation of a behavioural disorder. Family and past medical history were uneventful. Parents were non consanguineous. Cognitive dysfunction prevailed at this early stage with an attentional deficit and learning difficulties, outlined in an extensive neuropsychological profile. At the age of 9, he presented with atypical absences and myoclonic seizures, and antiepileptic therapy was initiated.
Progressive motor and cognitive deterioration followed, with, by the age of 12, global aphasia, memory and attention deficits, motor dysfunction with altered gait, falls and assistance required in all activities of daily living.

Results:
Electroencephalogram readings showed diffuse slowing with 4Hz notched delta waves and bursts of generalized spike waves. Decreasing amplitude of the background activity has not been noted. Magnetic resonance imaging revealed, from the age of 10 years, diffuse cortical and subcortical atrophy without deep nuclei or brainstem lesions. A brain PET-CT showed diffuse cortical hypometabolism without signs of tissue deposits. Electroretinogram and funduscopic examination were normal. Oto-acoustic emissions, audiogram and auditory evoked potentials were normal. Extensive and repeated blood investigations with metabolic panels, anti-neuronal autoantibodies, neuro-transmitters, and viral serologies for measles revealed no abnormalities. Metabolic urine and cerebrospinal fluid analyses were also normal. Abdominal ultrasound found no organomegaly. A muscle biopsy showed no histological or immunochemical markings. Culture of skin fibroblasts didn't yield any enzyme deficiencies and no abnormalities were found at electromicroscopy of leucocytes. An electroneuromyography ruled out signs of peripheral neuropathy or myopathy. Finally more than 1000 genes were studied including those involved in neuronal ceroid lipofuscinoses, PLA 2G6, Huntington, POLG1, and ASAH1, without a mutation identified.

Conclusion:
Five years down the line, with an extensive diagnostic work-up paralleling a progressive deterioration of his clinical (mostly cognitive and motor) state, we remain no further enlightened as to the cause of this child's condition. The next step in view is a brain biopsy. We would however benefit at this stage from other clinicians' feedback.

DCC2 DYSTONIE DES MAINS CHEZ UN ADOLESCENT CONNU POUR UNE DYSPRAXIE ORO-MOTRICE ET GESTUELLE

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Jeune homme de 14 ans suivi en neurologie pédiatrique dans le cadre d'un trouble sévère et développemental du langage oral et d'une dyspraxie gestuelle. Devant la difficulté de réaliser des praxies bucco-linguo-faciales et des gestes simples, un syndrome bioperculaire est initialement évoqué. L'apparition de postures dystoniques des mains, invalidantes, motive une réévaluation clinique. Le tableau est alors suggestif d'une entité rare qu'une investigation unique permet de confirmer.

Cette observation et son diagnostic seront discutés lors de la session de discussions des dossiers cliniques.

PTPN11 MUTATION ASSOCIATED WITH ANGELMAN SYNDROME: A COMPLEX PHENOTYPE. DESCRIP-TION OF THE FIRST CASE

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PTPN11 mutation associated with Angelman Syndrome: a complex phenotype. Description of the first case.

Purpose: highlight the importance of detailed study of electroclinical features in a pa-tient with double genetic anomaly.
Case: male. 7 years old. Delayed motor acquisitions and severe cognitive impairment with absence of language. The clinical phenotype is characterized by peculiar facial traits with hypertelorism with down-slanting palpebral fissures, ptosis and low-set posteriorly ro-tated ears with a thickened helix, bulbous nose and cardiovascular defects with pulmonary stenosis and DIA osmium secundum. The suspicion of RASpathy- Noonan syndrome was confirmed by the molecular analysis of PTPN 11 gene in the first year of life. The child carried out a missense mutation on exone 3 (Asn58Asp).
The epileptic history onset in the second year of life with prolonged tonic-clonic febrile seizures and daily atypical absences. The child underwent a polytherapy (valproate, ethosuccimide and clobazam) with incomplete response.
The interictal EEG pattern was characterized by diffuse, low background activity, diffuse and asynchronous slow waves with superimposed spikes and spike-waves on both hemispheres, that become continuous during sleep.
The ictal EEG pattern showed prolonged and diffuse and rhythmic
(1,5-2Hz) polyspikes-waves discharges or spike-slow waves discharges clinically associated with myoclonic seizures and atypical absences.

Discussion: the complex clinical profile with a very severe cognitive impairment and electroclinical phenotype disagree with the genetic diagnosis of Noonan syndrome, so became mandatory to make further studies in order to evaluate the presence of comorbilities.
The second genetic study (array-CGH) shows Array CGH: del 15q11q13:
Angelman Syndrome.

Conclusion: the case highlight the need of an accurate description of the electroclinical study and epileptic phenotype in order to have a correct diagnosis, a specific treatment and accurate information about the prognosis of epileptic disease.

P1 TREATMENT EFFECT OF IDEBENONE ON INSPIRATORY FUNCTION IN PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY

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Study Objective: Assessment of dynamic inspiratory function may provide valuable information about the degree and progression of pulmonary function decline in patients with Duchenne muscular dystrophy (DMD). The aims of this study were to characterize inspiratory function and to assess the efficacy of idebenone on this pulmonary function outcome in a large and well-characterized cohort of 10-18 year old DMD patients not taking glucocorticoid steroids (GCs) enrolled in the randomized controlled DELOS trial (Buyse et al., 2015).

Methods: We evaluated the effect of idebenone on the highest flow generated during an inspiratory FVC maneuver (maximum inspiratory flow; V'I,max(FVC)) and the ratio between the largest inspiratory flow during tidal breathing (tidal inspiratory flow; V'I,max(t)) and the V'I,max(FVC). The fraction of the maximum flow that is not used during tidal breathing has been termed Inspiratory Flow Reserve (IFR).

Main Results: DMD patients in both treatment groups of DELOS (idebenone, N=31; placebo: N=33) had comparable and abnormally low V'I,max(FVC) at baseline. During the study period, V'I, max(FVC) further declined by -0.29 L/s in patients on placebo (95% CI: -0.51, -0.08; p=0.008 at week 52), whereas it remained stable in patients on idebenone (change from baseline to week 52: 0.01 L/s; 95% CI: -0.22, 0.24; p=0.950). The between-group difference favoring idebenone was 0.27 L/s (p=0.043) at week 26 and 0.30 L/s (p=0.061) at week 52. In addition, during the study period, the IFR improved by 2.8% in patients receiving idebenone and worsened by -3.0% among patients on placebo (between-group difference 5.8% at week 52; p=0.040).

Conclusions: This study suggests that idebenone preserved inspiratory muscle function as assessed by V'I,max(FVC) and IFR in patients with DMD.

IDEBENONE REDUCES RESPIRATORY COMPLICATIONS IN PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY

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Study Objective: In DMD, progressive loss of respiratory function leads to restrictive pulmonary disease that evolves into severe respiratory complications. Of particular concern are ineffective cough, secretion retention and recurrent respiratory tract infections.
In a Phase 3 randomized controlled clinical trial (DELOS; Buyse et al., 2015), idebenone reduced the loss of respiratory function in DMD patients 10-18 years of age and not taking concomitant glucocorticoid steroids (GCs) over a 1-year study period.

Methods: In a post-hoc analysis of DELOS, "bronchopulmonary adverse events" (BAEs) were defined by a study-independent physician as bronchitis, pneumonia, upper respiratory tract infection, influenza and/or viral infection with respiratory symptoms, laryngitis, respiratory failure, acute respiratory failure, cough and dyspnea.

Main Results: More patients in the placebo group than in the idebenone group reported BAEs (placebo: 17 of 33 patients, 28 events; idebenone:
6 of 31 patients, 7 events). The Hazard ratios (HR) calculated "by patient" (HR 0.33, p=0.0187) and for "all BAEs" (HR 0.28, p=0.0026) indicated a clear idebenone treatment effect. The overall duration of BAEs was 222 days (placebo) vs. 82 days (idebenone). In addition, there was also a difference in the use of systemic antibiotics typically utilized for the treatment of BAEs. In the placebo group, 13 patients (39.4%) reported 17 episodes of antibiotic use compared to 7 patients (22.6%) reporting 8 episodes of antibiotic use in the idebenone group. Furthermore, patients in the placebo group used systemic antibiotics for longer (105 days) compared to patients in the idebenone group (65 days).

Conclusion: This post-hoc analysis of DELOS indicates that idebenone reduces the risk of bronchopulmonary adverse events and reduced the need for systemic antibiotics.

NON-PROGRESSIVE PUBERTY...DO NOT LOOK SO FAR

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We report a case of non-progressing puberty and secondarily short-stature in a 15-year old boy under chronic treatment with antipsychotic medicine.
He was referred, for the first time, in Pediatric Endocrinology Consultation by his neurologist who was concerned about the adolescent´s pubertal appearance.
The boy´s medical history is marked by autistic features, behavior troubles and learning difficulties and from the age of 12 4/12 years, he is under Risperidone treatment, with some improvement in his academic performance and behavior.
No family history of short stature and delayed puberty.
The boy is doing well, without any symptoms (notably headaches or visual disturbances).
His growth velocity was slowly going down over the 3 last years.
His actual anthropometric parameters are below the curves (_ P3 for weight and height) and the physical exam is normal, but is marked by under androgenization features and moderate gynecomastia. His pubertal development is quoted at Tanner stage II (testicular volume of 5 ml bilaterally, pubic hairs, but no axillary).
The biological check-up shows normal thyroid and adrenal function with gonadotropin-gonadal failure (LH 0,1 U/l, FSH 0,4 U/l, testosterone
0,10 ng/ml) in the context of marked elevation of prolactin (1161 mUI/l). The bone age is delayed (13 years) and consistent with pubertal maturation.
The retained diagnosis is medication-induced hyperprolactinemia with specific symptoms due to pituitary-gonadal inhibition.
A progressive discontinuation of the drug is underway and normally will restore prolactin level, achieve gonadotropic axis restoration and allow spontaneous puberty to proceed. A new clinical and biological evaluation will be done in 3 months and a particular attention will be paid to bone health. Hypogonadotropic hypogonadism, even if transient, could reduce the bone mass accrual and bone density in adolescents.
Pharmacologic hyperprolactinemia (usually symptomatic) and its inhibitory action on gonadotropic axis, with hypogonadotropic hypogonadism is the first endocrine side effects of antipsychotic drugs and should be kept in mind every time when such treatment is prescribed in pre pubertal/pubertal children. Risperidone is a combined serotonin/dopamine receptor antagonist that can cause substantial elevation in prolactin levels (higher than those caused by typical antipsychotics).

MOYAMOYA DISEASE- A RARE, BUT POSSIBLE DIAGNOSIS IN CHILDREN

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A 6-year-old girl was admitted in our Neurology Unit with repeated malaises associating a motor deficit (several episodes over the past
12 months, with acute motor deficit in the right arm and leg, dysarthria and no or very slight consciousness impairment). In evolution, the motor deficit seems to become permanent.
Pregnancy, birth, infancy and childhood development are uneventful.
Her medical past is unremarkable. No recent history of trauma, infection, travel, drug treatment. Family medical history shows several cases of epilepsy.
The general physical exam was normal, except for a heart murmur and the neurological exam showed a right hemiparesis.
First laboratory evaluation (haematological, renal, liver, electrolyte, glucose, acid-basic status) came back normal. 24 hours electroencephalographic recordings (EEG), the ophthalmic exam and the abdominal ultrasound were also normal. The cardiologic echography showed a mild supravalvular pulmonary artery stenosis. The first MRI showed left cortical and subcortical atrophy rolandic and peri- rolandic atrophy, suggesting ischemic sequels. The magnetic resonance angiography showed stenosis and occlusion of large intracranial vessels and the presence of collateral vasculature, image compatible with Moyamoya disease.
The additional genetic test (CGH- array) came back normal.
A conservative treatment with Aspirin 5 mg/kg/day was started. The patient didn't present any malaises since the beginning of the treatment.
The retained diagnosis is Moyamoya disease with isolated supravalvular pulmonary artery stenosis.
Moyamoya disease is a rare cerebrovascular disease, but should remain a differential diagnosis in children with repetitive ischemic attacks (clinically evoked by malaises with motor deficiency). Long term neurologic and radiologic follow-up is essential to prevent further stroke events and improve outcomes.

P5 NEURODEVELOPMENTAL PROFILE IN ANGELMAN SYNDROME: MORE THAN LOW INTELLIGENCE QUOTIENT

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STUDY OBJECTIVES: Angelman Syndrome (AS) is a rare neurogenetic imprinting disorder attributable to the reduced expression of the maternally inherited allele of UBE3A gene. The aim of the study is to provide a complete neuro-developmental profile in AS, with particular regard to some aspects, not so frequently analyzed in the literature, such as neurovisual and communicative features.

METHODS: so far a total of fifteen subjects aged from 3 to 16 years (6 males and 9 females) with molecular confirmed diagnosis of AS (with different genotypic mechanisms underlying) have been enrolled in our study. All of them underwent an assessment protocol including neurological and neurovisual examination and the evaluation of motor (Gross Motor Function Measure Scale), cognitive (Griffiths Mental Development Scale and Uzgiris Hunt Scale) and communicative (MacArthur Bates Communicative Development Inventory and video-recordings children's verbal expression) aspects.

RESULTS: All children presented motor function involvement and neurovisual impairment characterized by refractive errors, fundus oculi anomalies, visual attention disorder, strabismus and/or oculomotor dysfunction. A severe cognitive impairment was detected with different profiles according to the test applied. In all cases, communicative disability regarding phonemic inventory, word/gesture comprehension and production was revealed.

CONCLUSION: It is known that there is a correlation between neurofunctional profile and genotype, with deletion patients having worse outcomes than non-deletion.
The study underlined that AS patients present a complex neurodevelopmental profile in which several aspects play a negative role in global development leading to a severe functional impairment.
Among this we found out some peculiar aspects, that could be useful to better understand the real developmental profile and that could be integrate in the rehabilitation programs:
- An early correction of visual disorders can improve visual acuity
for activities of daily living and can promote the development of cognitive functions;
- In other neurological pathologies is documented a relation between
oculomotor impairment and attention deficit, therefore an early identification and promotion of oculomotor function may have a positive effect on attention deficit.
- Our study demonstrate that AS children present a gestural repertoire
and secondary intersubjectivity; this second point led us to sustain the think that that AS is not so strickly related to ASD.
- The use of UHS, which privilege a qualitative evaluation of
cognitive competences, is more reliable than the psychometric tools, because there are no direct indications, but only the elicitation of behaviours as a consequence of the presentation of a stimulus.

OCULAR MOTILITY DISORDER AND DEVELOPMENTAL DELAY: A NEW CASE OF SRD5A3 – CDG WITH A NOVEL MUTATION

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Background

Congenital disorders of glycosylation (CDG) are genetic diseases with an extremely broad spectrum of clinical presentations due to defective glycosylation of glycoproteins and glycolipids.

Over 100 human genetic disorders have been associated with abnormal glycosylation; because the defective genes are involved in a variety of functionally diverse metabolic pathways, the clinical presentation of CDG subtypes is highly heterogeneous. Defects in the biosynthesis of dolichol phosphate are an upcoming group of CDG and until now only thirteen children with this form due to mutations in the SRD5A3 gene have been described.

Clinical report

We report on a male of 38 months, came to our attention at the age of six months for nystagmus and roving eyes movements and developmental delay. He is the first child of healthy related Moroccan parents. No particular problems were referred during pregnancy, delivery ma fin dai primi mesi di vita il bambino presentava importanti problem of feeding problems and frequent discharges of faeces.

Because of these clinical features the child underwent several investigations: ophthalmic and neurophtalmologic evaluation with the evidence of a severe visual impairment associated to the ocular motility disorder; brain MRI showed cerebellar vermis hypoplasia, bilateral optic nerve hypoplasia and dysmorphic brainstem; clinical, serological and genetic investigation (HESX1) for excluding septo-optic displasya; karyotype and subtelomeric rearrangements, both negative; blood tests, which revealed hypercholesterolemia and elevated value of liver enzymes, associated with mild steatosis at the abdominal ultrasound.

These data led us to investigate CDG disorders; first of all we assessed the tIEF profile which resulted abnormal (confirmed by a second test) and the samples of this child were therefore analyzed in the context of CDG type 1 (CDG panel). The patient is homozygous for a mutation, never described before, in the SRD5A3 gene and his parents are carrier of the mutation.

Conclusions

Our patient presents a novel mutation in the SRD5A3 gene, but is clinically similar to those described in the literature. We want to stress the importance to consider this type of investigations in children with an association of ocular motility disorder, cerebellar hypoplasia and developmental delay, in order to better define the clinical presentation and the natural history of the disease.

P7 HYPOMYELINATING LEUKODYSTROPHIES: A POL3A NOVEL MUTATION IN TWO SIBLINGS OF PAKISTANI ORIGIN

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Background : Hypomyelinating leukodystrophies are rare diseases. There are five overlapping clinical phenotypes: 4H syndrome, ataxia, delayed dentition and hypomyelination (ADDH), tremor-ataxia with central hypomyelination (TACH), leukodystrophy with oligodontia (LO), hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum (HCAHC). Due to the heterogeneous phenotypes, diagnosis is still challenging.
We present two siblings of Pakistani origin (a 3 years old male and a
7 years old female) who were sent to our attention because of tremor with severe postural deficit and speech impairment.

Patients and methods
Case 1 : Motor delay was reported since the beginning. Clinical and neurological phenotype was consistent with horizontal pendular nystagmus, adjustment of the head, upper limbs tremor activated only by voluntary movement and gait ataxia (she was able to perform only 2-3 steps with two-hand support and subsequent fall), global muscular hypotrofia, mild plastic muscular hypertonia of lower limbs. Osteotendineous reflexes were preserved. She showed high-amplitude dysmetric movement during a reaching task. The speech was poor and poorly intelligible for the presence of dysarthria, she showed good understanding of mother-language.

Case 2 : The brother presented the same signs and symptoms, but less serious and disabling (he could perform autonomous walking with ataxic characteristics for some steps). Parents reported milder delay in motor acquisitions than his sister (sitting station at 8 months, deambulation at 24 months).

Results : During hospital stay the patients underwent to the following
examinations: blood tests, electroencephalography, visual evoked potentials, electroretinogram, brainstem auditory evoked potentials, electroneurography, electromyography, abdominal ultrasound, neurophtalmologic evaluation and brain MRI. All the instrumental examination were negative but the brain MRI, which showed involvement of supra/subtentorial white matter with partial savings of corticospinal bundles of optical and acoustic-way streets; moderate atrophy of corpus callosum, brainstem and cerebellum) in both siblings (the brother showed a lesser degree of atrophy), MRI findings and clinical phenotype allowed us to suspect a 4H syndrome. We studied the POL3A gene in both siblings and found omozygous mutation in c.1931A_G(p.E644G), not described in literature. Statistic studies showed this mutation as most likely patogenetic. Analysis on both parents is currently underway.

Conclusion : Our cases confirm the spectrum variety of 4H syndrome: our patients didn't show all typical signs of the disorder (particularly hypodontia and hypogonadotropic hypogonadism) and clinical phenotype was different in term of severity. This could be due to the young age of the siblings. Ataxia and MRI findings were essential for the diagnosis.

PARALYSIE BULBAIRE ET ATTEINTE NEUROSENSORIELLE : QUAND UNE VITAMINOTHÉRAPIE PEUT CHANGER LA DONNE

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But du travail : Les neuropathies héréditaires sensori-motrices représentent un groupe hétérogène de maladies, qui peuvent être associées à une atteinte sensorielle. Le syndrome de Brown-Vialetto-Van Laere (BVVL) en est une forme rare et évolutive.

Méthodologie : Nous rapportons l'observation d'une patiente qui présentait un déficit auditif sensoriel depuis l'enfance; vers l'âge de 12 ans des troubles de l'équilibration sont apparus; elle a été opérée d'une scoliose à 14 ans, puis un déficit visuel s'est installé progressivement à partir de 16 ans. Adressé à l'âge de 17 ans, la patiente présente alors une ataxie proprioceptive avec une neuropathie axonale, une atteinte bulbaire, un déficit moteur prédominant aux membres supérieurs, une neuropathie optique sévère, sans détérioration cognitive. En moins de 6 mois, son état neurologique se détériore dramatiquement, associant un handicap sensoriel sévère et un handicap moteur majeur limitant l'autonomie et nécessitant une ventilation sur trachéotomie et une alimentation par gastrostomie.

Résultats : Huit mois après la mise en place de la supplémentation en Riboflavine (vitamine B2), la patiente est sevrée de la ventilation invasive, elle s'alimente par voie orale, elle est autonome pour les gestes usuels, tient assise seule, effectue ses transferts. Son acuité visuelle est nettement améliorée, et elle peut reprendre sa scolarité. L'étude génétique a montré l'existence de deux nouvelles mutations hétérozygotes du gène SLC52A2.

Conclusion : Le tableau clinique associé au syndrome de BVVL est caractérisé par une neuropathie auditive, une ataxie proprioceptive, une paralysie bulbaire, et une neuropathie optique. Certains patients peuvent présenter un profil des acylcarnitines évocateur de déficit multiple en acyl-CoA déshydrogénases. Les troubles du transport et du métabolisme de la riboflavine constituent un groupe de pathologies dont les bases moléculaires sont en cours de démembrement, qui se caractérisent par une polyneuropathie avec atteinte sensorielle, et qui représentent une des rares formes de pathologies neuromusculaires traitables.

SUDEP DISCLOSURE IN PAEDIATRIC EPILEPSY: AN ITALIAN SURVEY ON "TO SAY OR NOT TO SAY"

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BACKGROUND AND OBJECTIVES.
Sudden unexpected death in epilepsy (SUDEP) is a syndrome where a person with epilepsy dies suddenly and no other cause of death is found. During recent years a lively debate has been surrounding about the importance of disclosing the SUDEP risk . Professional societies and clinical practice guidelines recommend to disclose the risk of SUDEP as part of the comprehensive epilepsy education. Aim of this study is detecting if medical professionals dealing with paediatric epilepsy disclose or not the risk of SUDEP to parents of affected children in an Italian context.

METHODS.
On September 2015 (and up until December 2015), a call for on-line questionnaire on SUDEP has been sent to 556 Italian neuropediatricians. The questionnaire detected both socio-demographic data and attitudes towards SUDEP. Chi-squared test or multivariate logistic regression was performed as appropriate. An additional qualitative analysis (Interpretative Phenomenological Analysis) is ongoing.

FINDINGS.
One-hundred and fourteen (20.5%:71F,43M;age-range:24-71years; m.a.46.15;SD=11.91) answered to the questionnaire. To the question on the own belief on counselling about SUDEP, 18 (16.2%) respondents stated that it should be done with all patients and 22 (19.8%) with the majority, 58 (52.3%) with the minority, and 13 (11.7%) with the minority. To the question if respondents counselled SUDEP to their patients, only 2 (1,8%) counselled all patients, 28 (25%) none of the patients, 71 (63,4%) the minority and 11 (9,8%) the majority. We found a discrepancy between the number of neuropediatricians who believe it is right to counsel and the number who effectively counsel (p=.002). Factors associated with "not counselling SUDEP at all" in univariate logistic regression were: low number of epileptic patients (p<.01), less years of experience (p=.03) and thinking to be safe from a legal point of view (p<.001). In multivariate analysis, only "I examine occasionally epileptic patients" predicted independently that SUDEP was not discussed at all (p=.006). The main reason for counselling on SUDEP was the refractory course of disease (79%) and patient demanding information (65%). From qualitative analysis, we can highlight the emotional difficulties of neuropediatricians to handle with SUDEP disclosure.

CONCLUSIONS.
A minority of neuropediatricians counsel all of their patients in Italy. Independent predictors of not discussing SUDEP at all were a small number of years of practice, a small number of patients and legal issues. Refractory epilepsy and parents' demanding the main reasons to counsel on SUDEP. Educational training may help neuropediatricians in handling this difficult communication issue.

CORTICOSTEROID THERAPY IN CONTINUOUS SPIKE AND WAVE DURING SLEEP SYNDROME

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Introduction: Continuous spike and wave during sleep epileptic encephalopathy (CSWS) is a rare condition characterized by seizures, speech alterations and cognitive impairment in association to spike and wave status epilepticus during sleep (ESES). Seizures in most patients begin during childhood and are sometimes refractory to conventional anticonvulsive medication. Additionally, cognitive and electroencephalographic deterioration are often seen despite treatment. Following its original description in 1971, several therapeutic schemes have been tested without thus far achieving universal consensus. In this context, immunomodulation recently emerged as a potentially beneficial adjunctive therapy for refractory CSWS.

Objective: To describe the response to corticosteroid therapy in a small series of patients with CSWS refractory to conventional antiepileptic drugs.

Materials: We retrospectively analysed medical records from three patients:
Patient 1: female, first seizure at eight years, after since under conventional antiepileptic regimen. The patient posteriorly developed progressive detriment of academic performance and language skills. Electroencephalogram (EEG) showed CSWS pattern. The patient underwent five months steroid therapy with excellent clinical evolution. After treatment withdrawal the patient suffered a relapse. One year of additional immunomodulation was then administered. Posterior EEG control: normal. Clinical evolution: favourable.
Patient 2: male with speech alterations beginning at five years followed by seizures onset one year after. Conventional antiepileptic treatment was established. Afterwards, at age eight, the patient presented drastic language deterioration and diurnal sleepiness. He underwent five months of steroid therapy with positive response. Electro-clinical evolution in posterior control: favourable.
Patient 3: female, first seizure at eight years of age with normal peri-ictal EEG studies. Conventional antiepileptic treatment was then started. Two years after, the patient developed an encephalopathic syndrome with prominent speech alterations. Electroencephalogram at that moment showed CSWS pattern. The patient underwent intravenous immunoglobulin administration without clinical or EEG response. Long term corticotherapy was indicated with favourable clinical response despite persistent CSWS pattern. Incorporated additional therapy with Sultiame leaded to an EEG remission. Following steroidal therapy withdrawal, the patient presented a relapse under Sultiame in association to conventional antiepileptic drugs. Immunomodulation was then re-established.

Conclusions: Despite the clinical heterogeneity at baseline, favourable outcomes were observed following long term immunomodulation with corticosteroids in patients with refractory CSWS. Association to Sultiame provided a faster response in one patient. This effect, however, was not sustained after immunomodulatory withdrawal. Long term immunomodulation with corticosteroids might provide an effective and well tolerated therapeutic alternative in patients with refractory CSWS.

DRAVET'S SYNDROME: GENETICALLY CONFIRMED CASE SERIES

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Introduction: Dravet's Syndrome (DS) constitutes a clinically challenging epileptic encephalopathy of early debut and progressive impairment. This entity typically appears during the first year, with prolonged febrile and afebrile, clinically heterogeneous epileptic seizures, regularly associated to specific triggers. Higher cerebral functions are afterwards compromised resulting in motor, intellectual, speech and developmental impediments. From within the spectrum of genetic mutations recognized in DS, the SCN1A gene (which encodes for a voltage dependent sodium cannel subunit) is the most commonly affected. Mutations in this gene produce a widespread of functional alterations in the transcribed proteins that determine the clinical repercussion.

Objective: To describe the electro-clinical evolution in relation to genetic mutations found in a series of clinically diagnosed DS patients.

Materials and Methods: Medical records from seven patients with an a priori clinical diagnosis and posterior genetic confirmation of DS were retrospectively analysed.

Results: Seven patients were included (three females and four males). The mean age at debut of epileptic seizures was 5.3 months (SD +/- 2.5) corresponding to febrile seizures in six patients (86% $p<0.008$) which were posteriorly accompanied by non-febrile episodes. Clinically, seizures were both generalized (tonic-clonic, myoclonic, and absences) and focal. All patients presented at least one episode of status epilepticus. Commonly described seizure triggers included: infections, high environmental temperatures and photosensitivity. Electroencephalographic alterations were heterogeneous and fluctuating. All patients had normal brain Magnetic Resonance Imaging scans. Although normal at debut, neurodevelopment was subsequently compromised within evolution in all patients resulting in severe disability in five. Mainly affected areas were conduct, language and motor skills. Therefore, additional pharmacological and multidisciplinary care was required. All of the patients' treatment regimens underwent several necessary modifications during the course of the disease. Genetic testing revealed several types of SCN1A mutations. Mutation types and its associated key clinical findings were: nonsense – sudden death (1 patient), missense – refractory epilepsy (2 patients), frameshift – myoclonic and absence seizures (2 patients) and intronic - lesser degree of disability (2 patients).

Conclusion: Management of DS is challenging, and a multidisciplinary approach is recommended. As in the literature, complementary testing in this sample resulted in diverse and sometimes fluctuating results. Thereafter, even if precise genotype-phenotype correlations cannot so far be established, genetic testing remains useful considering that mutation types possess prognostic value. Notably, patients with intronic mutations of the SCN1A gene presented the least incapacitating evolution within this progressively devastating, clinically heterogeneous entity.

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L'apprentissage des mathématiques
Des difficultés aux interventions

L'objectif de la présentation est triple :

1) Présenter un état de l'art des connaissances disponibles relatives aux difficultés d'apprentissage des mathématiques chez les enfants de
3 à 12 ans, notamment des sources potentielles de difficultés et leurs poids respectifs. Ces connaissances reposent sur un nombre limité de modèles, le principal étant celui du Triple code (Dehaene & Cohen, 1992 et plusieurs révisions) ;

2) Illustrer la manière dont ces connaissances ont conduit à l'élaboration d'outils diagnostiques pour la période considérée (UDN ; TEDI-MATHS ; ZAREKI). Plusieurs de ces outils seront évoqués ainsi que les conceptions théoriques qui les sous-tendent ;

3) Montrer que la période récente a vu apparaître des outils et programmes d'intervention visant à la prévention ou à la remédiation des difficultés. Seront évoqués certains de ces outils, notamment ceux qui ont donné lieu à l'évaluation de leurs effets. Les perspectives de développement de ces outils seront évoquées.

DYSLEXIE / DYSLEXIA

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Dyslexia is a specific learning disorder with impairment in reading (DSM-5) affecting 3–6% of the population. It is characterised by difficulties with accurate and/or fluent word recognition and by poor spelling and decoding abilities. These difficulties occur despite adequate cognitive abilities and educational opportunities, in the absence of neurological and sensory deficits, but causing a major limitation for some activities of daily living.

Dyslexia is a neurodevelopmental disorder with a biological origin that is the basis for abnormalities at a cognitive level that are associated with the behavioral signs of the disorder. The biological origin includes an interaction of genetic, epigenetic, and en vironmental factors, which affect the brain's ability to perceive or process verbal or non verbal information efficiently and accurately.

The learning difficulties are persistent, not transitory. In children and adolescents, persistence is defined as restricted progress in learning (i.e., no evidence that the individual is catching up with classmates) for at least 6 months despite the provision of extra help at home or school.

The individual's performance of the affected academic skills is well below average for age. Academic skills are distributed along a continuum, so there is no natural cutpoint that can be used to differentiate individuals with and without specific learning disorder. Thus, any threshold used to specify what constitutes significantly low academic achievement (e.g., academic skills well below age expectation) is to a large extent arbitrary. Low achievement scores on one or more standardized tests or subtests within an academic domain (i.e., at least 2 standard deviations below the population mean for age, or below the 5th percentile) are needed for the greatest diagnostic certainty.

Dyslexia commonly co-occurs with other neurodevelopmental disorders (e.g., ADHD, communication disorders, developmental coordination disorder) or other mental disorders (e.g., anxiety disorders). These comorbidities do not necessarily exclude the diagnosis of specific learning disorder but may make testing and differential diagnosis more difficult, because each of the cooccurring disorders independently interferes with the execution of activities of daily living, including learning.

In many countries (e.g Italy) the law protects the right to education of dyslexic children and gives the school an opportunity to reflect on the methods to be implemented to encourage all students, giving space to their true potential according to their peculiarities. The law defines the right of the student with SLD to benefit from special measures and compensatory educational flexibility during school and university studies.

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Studies have shown high rates of comorbid conditions among children with ADHD, including oppositional defiant disorder, anxiety/mood disorder, learning disabilities, severe tics disorder. For this reason, diagnosing ADHD includes assessing the child for comorbid conditions. Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD): are more common in children with ADHD. Most children ADHD refuse to do what adults want them to do: these behaviors are part of normal development but if they continues for a long time, the child may have ODD, or a more severe condition CD. ODD & CD are common in children with hyperactivity and impulsivity. ODD commonly persists into adulthood. Mood disorders (anxiety or depression): Some studies suggest that anxiety and depression are more common in children with symptoms of inattention. Girls are slightly more likely than boys to have a comorbid anxiety disorder. Children with depression "carry the world on their shoulders". They rarely talk what is bothering them.

Learning disabilities (LD): children with ADHD very often have a comorbid learning disability. They have normal intelligence but have weaknesses in working memory and executive function; LD refers often to a deficit understanding or using spoken or written language. This underlying deficit will show itself in problems with listening, thinking, speaking, reading, writing or doing mathematical calculations.

Developmental Coordination Disorder (DCD): DCD is suspected when a child has motor coordination that is much poorer than expected from the child's age and intelligence; they may clumsy and often drop things; they may do poorly at sports. They may have trouble getting dressed or riding bicycle.

Severe tics / Tourette'syndrome: While children with ADHD often act impulsively, children with Tourette'syndrome have tics which they are unable to control. Most children with Tourette'syndrom also meet criteria for a diagnosis of ADHD. It has been suggested that Tourette'syndrome may be a severe form of ADHD.

Mental health conditions: % of children ADHD who have comorbid condition

Oppositional Defiant Disorder	40 to 60%
Anxiety/mood disorders	25 to 48%
Conduct Disorder	14 to 20%
Severe tics: Tourette Disorder	11%

Learning disabilities: % of children ADHD who have comorbid condition

Reading disorder	15 to 40%
Mathematics disorder	10 to 25%
Dev. Coordination Disorder	40 to 60%
Oral language disorders	8 to 30%

The comorbidity increases risk for ADHD symptom severity and poor longitudinal outcomes. Effective treatment of ADHD will help treat comorbid symptoms when both occur. Behavioral therapies are often provided in accompaniment with psychopharmacological interventions to optimize treatment for the child with ADHD and ODD. The management of ADHD with mood disorders associate appropriate child psychiatry referral and psychopharmacology.

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DEVENIR À L'ÂGE ADULTE DES TROUBLES SPÉCIFIQUES DU LANGAGE ET DE LA MOTRICITÉ

Y. Chaix

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Au sein des troubles du Neurodéveloppement (DSM-5), les troubles spécifiques du langage (Trouble Spécifique du Langage 0ral et Dyslexie Développementale) ou de la motricité (Trouble d'Acquisition de la Coordination), constituent des motifs fréquents de consultation en Neurologie Pédiatrique. La prise en charge de ces troubles est relativement récente et les études concernant le devenir à moyen (Adolescence) ou long terme (Adulte) des enfants dans cette situation sont encore peu nombreuses. L'objectif de cette présentation, à partir de données existantes dans la littérature, est de répondre à trois questions: Les difficultés linguistiques ou motrices que présentent les enfants, persistent-elles à l'âge adulte ? Ces troubles ont-ils un impact sur le devenir académique ou professionnel des enfants ? Quelles en sont les conséquences socio-émotionnelles ?

Quelque soit le trouble envisagé (Trouble Spécifique du Langage 0ral, Dyslexie Développementale ou Trouble d'Acquisition de la Coordination) les études confirment la persistance des difficultés à l'âge adulte chez une majorité des sujets, avec un écart avec les sujets au développement typique qui persiste malgré les prises en charge et la maturation cérébrale. Les troubles ont également en commun des répercussions socio-émotionnelles, se manifestant notamment par des symptômes anxio-dépressif avec un impact sur la qualité de vie de ces personnes. La persistance du trouble et ses conséquences socio-émotionnelles contribuent à l'entretien de « spirales négatives ».

Les conséquences académiques, professionnelles voir médicales sont plus spécifiques à chacun des troubles : ainsi la majorité des sujets dyslexiques parviennent à compenser leur trouble et poursuivent des études, certes plus longues avec des aménagements, mais de même niveau que les sujets au développement typique; les sujets avec Trouble Spécifique du Langage 0ral font moins souvent des études secondaires et s'orientent professionnellement vers des emplois où l'exigence de la maitrise du langage ou le niveau d'alphabétisation sont moindres; de plus des études longitudinales soulignent des difficultés dans les interactions sociales chez ces sujets à plus long terme; enfin les enfants avec Trouble d'Acquisition de la Coordination se détournent de certaines carrière scientifiques mais sont surtout exposés sur un plan médical à un risque accru d'obésité et de problèmes cardio-vasculaire.

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L'APPORT DE LA RÉGION DU GOTHARD DANS LES SCIENCES EUROPÉENNES

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Airolo, président de la Fondation Centre Biologie Alpine Piora, Université de Genève

Combien les Alpes ont contribué à faire avancer les sciences? Nous considérons un cas spécifique: le col du St. Gothard et le Val Piora où nous avons un Centre de Biologie Alpine (CBA); une Fondation constituée par les deux Universités de Genève et Zürich et le Canton du Tessin. Dans le domaine des sciences naturelles il existe une bibliographie de 400 titres.

Les sciences naturelles : Le 18 et 19e siècle ont été marqués par un certain nombre d'explorations scientifiques, dans les domaines les plus divers. A l'échelle européenne on découvre, on décrit, on analyse avec de plus en plus de précision le cadre de la nature. La dynamique des connaissances est très active en Suisse dans certaines régions alpines en particulier dans le massif du St. Gothard. Le XVIIIe siècle a été défini par l'historien E. Motta «le siècle caractérisé par le grand nombre de naturalistes arrivés pour étudier le St. Gothard». Plus tard, à la fin du XIXe siècle, dès la naissance de la biologie des eaux douces comme discipline en Europe, la région de Piora a servi de base pour des travaux de recherche dont il faut souligner la systémicité et l'originalité. En effet, pour la limnologie science de synthèse, une région riche en eau, le massif du St. Gothard, la «mater fluviorum» européenne, et notamment le Val Piora, ont constitué l'écosystème hydrobiologique modèle.

Les sciences de l'ingénieur : Outre les études des naturalistes, le premier percement d'un tunnel sous le St. Gothard (1872-1882) va créer une dynamique de recherches dans les domaines les plus varié et parfois inattendus. Par exemple J.D. Colladon (1802-1893) collaborateur d'Ampère ingénieur conseil de l'entreprise Favre, spécialiste des techniques de percement, était prof. à l'Ecole centrale des Art et Métiers à Paris. La construction du barrage du Ritom (1914-1918) pour l'électrification de la ligne du St. Gothard porte à la découverte de l'état méromictique crénogénique. Ce phénomène rare, encore présent dans le Lac de Cadagno, fait l'objet de nombreuses recherches actuelles au CBA.

La parasitologie : Lors du percement du premier tunnel nous avons enregistré aussi un apport inattendue au progrès des connaissances en parasitologie. Selon la tradition orale : «les ouvriers avaient le sang qui se transformait en eau» c'était l'anémie du St. Gothard. L'ankylostomiase, maladie tropicale décrite au cœur des Alpes ou maladie des tunnels provoquée par Ancylostoma duodenale. Parasitose qui à l'époque (1880) a engendré des controverses: épidémiologique, clinique et de thérapie, mais surtout les études au Gothard ont indiqué la possibilité d'assainir les tunnels et ont constitué les premiers pas de la santé au travail et de la médecine du travail.

La géologie : En juin 2016 l'ouverture de l'Alp-Transit (tunnel ferroviaire de 57 km sous le St. Gothard) constitue un nouveau succès de la science et de la technologie, surtout si on pense aux difficultés géologiques que l'on craignait pour traverser la filon dolomitique de la «Piora-Mulde».
Pour conclure, Denis de Rougemont dans son livre «Quand je me souviens – c'est l'Europe» (1940) synthétisait la philosophie du St. Gothard : Monté hier au Gothard… ce haut lieu de la Suisse, ce vrai cœur de l'Europe… pour la première fois j'avais senti l'Europe… Je me disais en redescendant: «les suisses… savent-ils qu'ils ont au Gothard un haut lieu non pas seulement un tunnel et des forts?»

S. Bölte
Stockholm

Autism, first described by Leo Kanner and Hans Asperger, has historically gone through several conceptual changes. Recently, autism and related disorders have been redefined and grouped as autism spectrum disorder (ASD) under the new neurodevelopmental conditions umbrella of DSM-5. ICD-11 is now expected for 2017 and planned to widely follow DSM-5's description of ASD. In the last decade, ASD has been increasingly diagnosed, posing significant challenges to health care and educational services. Rising diagnoses rates are probably owing to many factors, but predominantly those related to broadening of diagnostic views, diagnostic substitution processes and expectancies of health and functioning. However, to a minor degree perhaps also biological factors, such as parental age. The etiology and phenotype is heterogeneous in ASD, and its origins complex, with latest evidence suggesting equally strong genetic and environmental factors. However, the exact nature of their effects and interaction in individual cases is still unclear. On the neurobiological level ASD is associated with local neural hyperconnectivity of distal neural hypoconnectivity as well as alterations of the social brain. Neuropsychologically, ASD is characterized by executive malfunction, attention to detail, and lacking social cognition. For the assessment of ASD, well standardized instruments have been developed, and a multitude of professional societies and national health care authorities use guidelines to improve services. ASD is currently incurable, although treatable to varying degrees to prevent worse outcomes. In conclusion, even though our understanding of ASD has markedly grown, the disorder still remains enigmatic in many aspects and outcome is poor for many being affected. In this lecture, I will provide a general update of ASD, give examples of my own latest research and others recent findings and envisage significant future developments in the field.

Sven Bölte is professor of child and adolescent psychiatric science at the Department of Women's and Children's Health, Karolinska Institutet (KI), and clinician at the Division of Child and Adolescent Psychiatry in Stockholm, Sweden. He is director of the unit for pediatric neuropsychiatry and director of the Centre of Neurodevelopmental Disorders at KI ("KIND"). Professor Bölte is editor of AUTISM, the Scandinavian Journal of Child and Adolescent Psychiatry and Psychology, and associate editor of the Journal of Autism and Developmental Disorders. He is has published more than 200 original articles, reviews, book chapters, assessment and intervention tools in the field of autism spectrum disorder and other neurodevelopmental disorders, and has been cited about 9000 times.

LES SIGNES PRÉCOCES DES TROUBLES DU SPECTRE AUTISTIQUE

P. Visconti
Centre for Autism Spectrum Disorders, IRCCS, Institute Neurological Sciences, Bologna, Italy

A l'échelle internationale, les troubles du spectre autistique (TSA) représentent aujourd'hui, avec le retard mental, l'une des formes les plus courantes des troubles du développement (DSM-5, 2013). L'incidence des TSA a eut une croissance exponentielle depuis les années 1970, passant d'environ 4-6 naissances sur 10000 à une naissance sur 68 en 2014. Cette récente hausse de la prévalence de l'Autisme peut être en partie expliquée par les changements dans le dépistage et le diagnostic, sans pour autant exclure l'impact potentiel des facteurs environnementaux et épigénétiques.
Alors que le dépistage met en évidence les signes qui pourraient être prédictifs de l'autisme, le diagnostic a quant lui pour objectif d'identifier le trouble. Le diagnostic précoce a notamment pour intérêt de démarrer le plus tôt possible une prise en charge de l'enfant avec sa famille. Et aujourd'hui, on sait que les accompagnements éducatifs sont d'autant plus efficaces qu'ils sont démarrés précocement.
Les premiers signes des troubles du spectre de l'autisme se manifestent chez l'enfant avant l'âge de 3 ans, et dans presque tous les cas avant l'âge de 2 ans. Il s'agit de difficultés dans les domaines socio-comunicatifs, l'apparition d'intérets et de comportements répétitifs, des atypies motrices et l'altération de la régulation de l'attention et des émotions. Recemment, l'existence d'une asimétrie dans la posture statique et dynamique a été montrée chez les bébés de 5 mois recevant plus tard un diagnostic d'Autisme.
L'analyse de films familiaux ainsi que le suivi longitudinale d'enfants à développement atypique ont en outre permis de confronter la manifestation des signes précoces chez les enfants avec autisme et chez les enfants présentant un retard de développement. Dans le but de différencier au plus tôt les trajectoires de développement, les résultats de ces études démontrent que dès la première année, les enfants avec Autisme se distinguent des enfants typiques par la présence d'atypies dans le domaine socio-communicatif. Un diagnostic différentiel distinguant les enfants avec Autisme de ceux présentant un retard de développement ne pourra être posé qu'à partir de la deuxième année lorsqu'une lente progression commencera à apparaitre chez ces derniers tandis que les difficultés d'ordre social et comunicatif seront plus prononcées chez les enfants atteints d'Autisme.

Une meilleure définition de l'expression phénotypique des TSA doit nécessairement porter l'attention vers les enfants montrant certaines atypies et difficultés et inviter au monitorage de leur trajectoire de développement. Une intervention précoce mise en oeuvre pendant la période de plasticité cérébrale, apanage des premières années de vie, pourrait jouer un rôle crucial dans la prévention de la manifestation d'un cadre complet d'Autisme.

N. Hadjikhani
Boston

Autism Spectrum Disorders (ASD) are neurodevelopmental conditions that have neural signatures, observable with anatomical and functional MRI. In my presentation, I will show results showing that anatomical differences can be observed in the white and in the gray matter of high-functioning individuals with ASD. I will also show examples of functional studies where ASD are diametrically opposed to typically developing individuals (TD) in brain activation (for a task of joint attention), or are surprisingly similar to TD (for a task probing affective empathy). Finally, I will present data from a pilot proof-of-concept study using a novel treatment for ASD and show how social cognition can be improved by this approach.

AUTISM SPECTRUM DISORDER FOR THE PAEDIATRIC NEUROLOGIST

A. O'Hare
Londres

This presentation will explore conditions that confer an increased risk of autism spectrum disorder, coexisting disorders and the differential diagnosis in paediatric neurology practice. There will be a focus on regression in the context of ASD, the interpretation of motor stereotypies and development and unusual sensory behaviours that can cause diagnostic confusion. Drawing on the evidence base from recent UK guidelines and a national study of ASD in Scotland, an indication of the findings for paediatric neurology practice will discussed.

Biography : Anne O'Hare is a Professor in Child Life & Health, Clinical Sciences, University of Edinburgh and Director of the newly established Salvesen Mindroom Centre for children with learning difficulties including autism spectrum disorder.
She is an honorary consultant paediatrician at the Royal Hospital for Sick Children, Edinburgh working in neurodisability and particularly communication disorders. She co-led the Scottish Intercollegiate Guideline 98 "Assessment, diagnosis and clinical interventions for children and young people with autism spectrum disorders" and the updated guideline which will be published this year. She is associate editor for Developmental Medicine & Child Neurology and for the forthcoming edition of Aicardi's International Textbook of Neurology, where she is author of the chapters on hearing and vestibular function, speech and language impairments, and autism spectrum disorders. She introduced Autism Diagnostic Observation Training into Scotland, established the Scottish ADOS and clinical ASD training programme with Dr Anne Gilchrist, Child & Adolescent Psychiatrist and has developed this programme with a wide range of colleagues in different disciplines throughout Scotland. This initiative has recently been awarded funding from the Autism Innovation & Development fund and NHS Education Scotland to create a national resource for clinician training and continuing professional development. Her research interests include autism spectrum disorder and coexisting conditions and the implications of complexity for diagnostic assessment.
Autism Spectrum Disorder, Specific Language Impairment and Motor Skills
All individuals with autism spectrum disorder experience some difficulty to some degree in how they have developed or use their speech and language in communication and many have coexisting problems with the control and process of movement and the closely associated sensory perception. Both the SIGN and NICE guidelines identify neurodevelopment conditions including specific language impairment, intellectual disability and developmental coordination disorder/dyspraxia as forming the principal non-neuropsychiatric differential diagnoses of autism spectrum disorder.
Prof Anne O'Hare will discuss these aspects, particularly as they confer complexity to the diagnostic process and intervention and will draw from her research and clinical experience to illustrate the issues. She will also cover the rare but important differential diagnoses that can be heralded by regression in communication and how neurodegenerative conditions, including Rett disorder and Landau Kleffner dysphasia, can sometimes mimic autism spectrum disorder. She will also discuss unusual, isolated conditions in motor stereotypies, sensory behaviour and restricted repetitive behaviour, that may cause confusion when interpreting a clinical presentation.

J. Campistol
Hôpital Sant Joan de Déu, Barcelone

La macrocéphalie est définie comme la croissance du périmètre crânien (PC) (mesurée au niveau fronto-occipitale) au-dessus du 98e percentile pour l'âge ou 2 déviations typiques (SD) au-dessus de la moyenne pour l'âge chronologique.
Il est important d'évaluer non seulement le PC comme un fait isolé mais ont doit toujours chercher la corrélation avec les paramètres globales de croissance, c'est à dire le poids et la taille de l'enfant. Ainsi, si ces trois paramètres se situent au-dessus du 98e percentile nous ne serons pas vraisemblablement face à une situation pathologique. En outre, il faut le comparer avec les mesures des parents.
La mesure de la tête est étroitement liée au volume du cerveau (substance grise et blanche) , à la quantité de liquide céphalorachidien , espaces de la convexité et os du crâne.
Parfois la macrocéphalie est présente depuis la naissance, le PC se maintient dans le même percentile et l'enfant montre un développement normal. Dans ce cas, le pronostique est bon mais il faut faire un suivi de l'enfant. A cet égard, il faut distinguer entre un enfant avec macrocéphalie stable dans le temps dans le même percentile et sans symptômes neurologiques, d'un enfant ayant un PC normal à la naissance mais qui augmente rapidement de percentile avec ou sans symptômes neurologiques.
Face à un enfant avec macrocéphalie les suivants éléments vont nous indiquer le besoin de poursuivre avec les explorations complémentaires (essentiellement neuro-imagerie): 1) l'évolution de l'anthropométrie et le PC, 2) l' histoire familiale (anthropométrie et PC des parents, antécédents familiaux d'hydrocéphalie), 3) l'examen physique et neurologique (signes cliniques d'hypertension intracrânienne, présence de spasticité, visceromegalie, phénotype anormale, regression neurologique, etc.) et l'évaluation du fond d'œil (présence d'un œdème papillaire, hémorragies rétiniennes, atrophie optique); 4) et notamment de l'évolution clinique.
A l'heure actuelle face à un enfant présentant fontanelle ouverte, nous devons considérer la pratique de l'échographie crânienne transfontanellaire car c'est une exploration facile à réaliser et qui nous permet d'écarter ou de confirmer une éventuelle hydrocéphalie externe, une vraie hydrocéphalie, la présence de malformations ou des kystes intracrâniens ou encore des collections extra-cérébrales.
Lorsque la fontanelle est fermée l'examen de choix est l'IRM crânienne, malgré que la TAC puisse également être utile.
Chez un nourrisson avec une augmentation asymptomatique ou même symtomatique mais progressive du PC et avec des images d'hydrocéphalie externe surtout dans la fissure Sylvien il est conseillé d'exclure l'acidurie glutarique type I, en déterminant aux urines les acides glutarique et 3-OH-glutarique. Le diagnostic et traitement précoces de cette maladie peuvent permettre un développement de l'enfant tout a fait normal. Actuellement le dépistage néonatal élargi nous permet de faire un diagnostique précoce et de démarrer le traitement rapidement.
En conclusion devant cette situation il est très important la démarche diagnostique, la connaissance des examens complémentaires disponibles, la valeur de chaque exploration, et très spécialement le suivi clinique de l'enfant en cas de doutes. Nous avons développé un algorithme de diagnostique face aux enfants avec macrocéphalie.

C11 ABSTRACT OF THE LECTURE ON "MACROCEPHALIC CHILDREN: DOES NEUROIMAGING HELP FOR THE DIAGNOSIS?»

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Macrocephaly is a rather common problem in the daily clinical work of pediatric neurologists. It is defined as a head circumference two standard deviations or more above the mean for age, gender, and gestation, measured over the greatest frontal circumference. In children, macrocephaly may be caused by a myriad of different disorders such as hydrocephalus, cerebral edema, space-occupying lesions, subdural fluid collection, thickening or enlargement of the skull (or hyperostosis), and a truly enlarged brain or megalencephaly. The correct diagnosis in a child with macrocephaly is paramount for management, prognosis, and counseling of the affected family (recurrence risk). Neuroimaging plays a key role in the diagnostic work-up of macrocephalic children. Head ultrasonography in the neonate and computed tomography (CT) provides useful information about the ventricular size and brain parenchyma and extra-axial spaces. Magnetic resonance imaging (MRI), however, is the neuroimaging tool of choice for the diagnostic work-up of macrocephalic children. Conventional MRI sequences provide high-resolution anatomical images and allow a more detailed visualization and evaluation of the cortical mantle, white matter abnormalities, small lesions, and abnormalities in the cerebellum and brainstem, including neoplastic lesions. In addition, advanced (e.g. diffusion weighted/tensor imaging, 1H-magnetic resonance spectroscopy, and susceptibility weighted imaging) provide more functional information that increase the diagnostic value of MRI in macrocephalic children. In various children, neuroimaging findings allow to make a final diagnosis. Otherwise, neuroimaging findings together with history and clinical findings are helpful to plan further appropriate investigations and interpret their results. Based on clinical cases, this lecture will illustrate the role of conventional and advanced neuroimaging techniques in the diagnosis of various causes of macrocephaly in children.

Notes

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