

# 45<sup>ème</sup> REUNION

DE LA SOCIÉTÉ EUROPÉENNE  
DE NEUROLOGIE PÉDIATRIQUE

45<sup>th</sup> SENP MEETING

23.24.25  
MARS 2017

CME : 15 CREDITS

► Torino ◀

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# COMITÉS

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# Bienvenue à Turin

## Welcome to Torino

Chers amis,

Au nom du bureau de la Société Européenne de Neurologie Pédiatrique et du comité d'organisation, nous avons le plaisir de vous accueillir à Turin pour la 45<sup>ème</sup> réunion de la SENP. C'est avec grand plaisir que nous avons organisé ce congrès qui se déroule pour la première fois dans notre ville.

Les thèmes s'annoncent très intéressants : le cours sera consacré à la neurooncologie pédiatrique, la première journée sera dédiée aux maladies auto-immunes cérébrales et pendant la deuxième journée nous discuterons des maladies des noyaux gris. Nous remercions chaleureusement les orateurs de renommée internationale qui ont accepté de participer et d'apporter leur précieuse contribution scientifique.

Turin est une ville romaine riche en histoire, fondée en 28 avant Jésus-Christ, elle fut pendant des siècles le cœur du royaume de Savoie et plus tard le théâtre de l'unité nationale italienne en tant que première capitale du Royaume d'Italie en 1861. Ville de tradition industrielle, elle est le siège de la plus importante maison italienne de construction d'automobile, la FIAT.

Nommée la « ville magique », elle renferme de précieux trésors, des édifices religieux et civils raffinés, de nombreuses collections d'art ancien et moderne, des musées innovants mais aussi celui du cinéma situé à l'intérieur de la Mole Antonelliana, un des symboles de la ville. N'oublions pas le fabuleux musée Egyptien, le plus important au monde après celui du Caire pour la valeur et la quantité d'œuvres qui y sont conservées.

Entourée par un anneau de montagnes splendides, nichée au pied de la colline, elle se situe non loin de la mer ; de plus Turin est riche en parcs et jardins et elle est traversée par le Po, le plus long fleuve d'Italie. C'est une ville historiquement significative pour le développement des neurosciences, on peut citer entre autres les prix Nobel de Médecine Rita Levi Montalcini et Salvatore Luria.

Enfin n'oublions pas l'excellente gastronomie et viticulture de la ville et de sa région, le Piemonte.

Soyez les bienvenus à Turin!

Irène BAGNASCO & Piernanda VIGLIANO

Dear Friends,

On behalf of the European Paediatric Neurology Society and the Organizing Committee, we are delighted to be welcoming you to Torino for the 45<sup>th</sup> SENP Conference. It is with great pleasure that we have organized this conference, which is being held for the first time in our City.

The different themes are highly relevant: the course will be dedicated to paediatric neuro-oncology, the first day will focus on autoimmune brain diseases and during the second day we will discuss basal ganglia diseases. We would like to extend our heartfelt thanks to the international renowned speakers who accepted to participate and bring their precious scientific contribution. ..

Torino is a Roman town full of history, it was founded in 28 BC and for centuries was the heart of the Savoy kingdom. Later on it was the foundation of Italian national unity as the first capital of the Italian kingdom in 1861. The city has an industrial tradition, it boasts the headquarters of the greater Italian car manufacturer, FIAT.

Called the "magical city", it holds several treasures, refined religious and civilian monuments, several ancient and modern art collections, and innovating museums including the Cinema museum located within the Mole Antonelliana, one of the city's landmarks. Let us not forget the fabulous Egyptian museum, one of the most important ones second only to the one in Cairo in terms of value and quality of its contents.

Surrounded by a ring of splendid mountains, nestled at the bottom of a hill, it is not far from the sea. Furthermore, Torino is also rich in parks and gardens, set on the banks of the Po River, the longest river in Italy.

It is a historically significant city for the development of neurosciences, we can list among others the Nobel Prize for Medicine attributed to Rita Levi Montalcini and Salvatore Luria.

Finally, it is essential to mention the excellent gastronomy and wine culture in the town and the Piedmont region.

Welcome to Torino!

Irène BAGNASCO & Piernanda VIGLIANO

# ► **SOMMAIRE** ◀

## **AGENDA**

p.5	<b>PLANNING</b>	Program at a glance
p.6-10	<b>PROGRAMME</b>	Program
p.6	Jeudi 23 mars	Thursday, March 23 <sup>rd</sup>
p.7	Vendredi 24 mars	Friday, March 24 <sup>th</sup>
p.9	Samedi 25 mars	Saturday, March 25 <sup>th</sup>
p.11	<b>POSTERS</b>	
p.13	<b>C.M.E</b>	
p.15	<b>INSCRIPTION</b>	Registration
p.16	<b>ACCES Turin</b>	To Torino
p.19	<b>RESUMES</b>	Abstracts

# ▶ PLANNING ◀

## JEUDI 23 MARS / THURSDAY, MARCH 23<sup>RD</sup>

COURS : NEURO ONCOLOGIE PEDIATRIQUE  
Pediatric Neuro oncology



- 14h00 **CONFERENCES / Lectures**
- 19h00 CONFERENCE INAUGURALE / Introduction lecture
- 20h00 Dîner de bienvenue / Welcome dinner

## VENDREDI 24 MARS / FRIDAY, MARCH 24<sup>TH</sup>



- 08h15 Accueil / Welcome
- 09h00 **MALADIES AUTO-IMMUNES / Auto immune diseases**
- 11h00 Communications Orales / Oral communications
- 13h30 **CONFERENCES / Lectures**
- 16h00 Communications Orales / Oral communications
- 16h30 **CONFERENCE / Lecture**
- 17h00 Projets de recherche / Research projects
- 18h00 Assemblée Générale de la SENP / SENP General Assembly
- 19h30 Visite culturelle et Dîner du congrès / Cultural visit and congress dinner

## SAMEDI 25 MARS / SATURDAY, MARCH 25<sup>TH</sup>



- 08h00 Meet the experts: Epilepsie / Epilepsy
- 09h00 Discussion de Dossiers Cliniques / Clinical cases discussion
- 11h00 **PATHOLOGIES DES NOYAUX GRIS / Basal ganglia disorders**
- 12h00 Visite des posters / Posters visit
- 14h00 **CONFERENCES / Lectures**
- 16h00 Communications Orales / Oral communications
- 17h45 Remise du prix du meilleur poster et de la meilleure CO / Award ceremony for best poster and oral communication

**Jeudi 23 Mars / Thursday March 23<sup>rd</sup>**

**COURS : NEURO ONCOLOGIE PEDIATRIQUE**  
**Course: Pediatric Neuro Oncology**

Modérateurs / Moderators : I. Bagnasco, F. Fagioli

- 14h00** | **Classification des tumeurs cérébrales pédiatriques / Classification of Pediatric Brain Tumors**  
C. Godfraind (Clermont-Ferrand, France)
- 14h30** | **Tumeurs du SNC : diagnostic et approches thérapeutiques / CNS tumors: diagnosis and therapeutic approaches**  
F. Fagioli (Torino, Italy)
- 15h00** | **Aspects génétiques dans la prise en charge des tumeurs cérébrales**  
Genetic aspects in the work-up of cerebral tumors  
V. Bours (Liège, Belgium)
- 15h30** | **Evolution du rôle de la neurochirurgie dans le traitement des néoplasies cérébrales / Evolution of the role of neurosurgery in the treatment of cerebral neoplasia**  
P. Peretta (Torino, Italy)
- 16h00** | **Pause / Coffee break**
- 16h30** | **Radio- et protonthérapies, toxicité tardive des traitements / Radio- and protontherapies, late toxicity of the treatments**  
F. Fagioli (Torino, Italy)
- 17h00** | **Place actuelle de la chimiothérapie / Current place of chemotherapy**  
D. Frappaz (Lyon, France)
- 17h30** | **Tumeurs du SNC et épilepsie : aspects cliniques et neurophysiologiques**  
CNS tumors and epilepsy: clinical and neurophysiological aspects  
P. Vigliano (Torino, Italy)
- 19h00** | **CONFÉRENCE INAUGURALE / INTRODUCTION LECTURE**  
**Pediatric psychopharmacology : at the intersection of neurology and psychiatry**  
Prof B.Vitiello (Torino, Italy)
- 20h00** | **Dîner de bienvenue / Welcome dinner**

## Vendredi 24 Mars / Friday March 24<sup>th</sup>

08h15 Accueil / Welcome

08h45 Mot de bienvenue / Welcome lecture

P. Leroy, Présidente SENP / SENP President

I. Bagnasco, Présidente du comité d'organisation / Organisation comitee President

### ► Maladies auto-immunes / Auto immune diseases

Modérateurs / Moderators : E. Fazzi, A. Bernabe Gelot

09h00 Maladies auto immunes et épilepsie / Auto immune diseases and epilepsy  
C. Korff (Geneva, Switzerland)

09h30 Interféronopathies à l'origine des atteintes inflammatoires cérébrales :  
aspects cliniques / Interferonopathies causing cerebral inflammatory lesions:  
clinical aspects

S. Orcesi (Pavia, Italy), E. Fazzi (Brescia, Italy)

10h00 Interféronopathies à l'origine des atteintes inflammatoires cérébrales:  
aspects génétiques et moléculaires / Interferonopathies causing cerebral  
inflammatory lesions: genetic and molecular aspects

M. Ae Lee Kirsch (Dresde, Germany)

10h30 Pause / Coffee break

### ► Communications orales / Oral communications

Modérateurs / Moderators : J-P. Misson, G. Gobbi

11h00 **O1** - Encephalopathies with intracranial calcifications in children: molecular  
and phenotypic characterization from multicentric series - D. Tonduti (Milano, Italy)

11h15 **O2** - Exploring autoimmunity in a cohort of children with Aicardi-Goutières  
syndrome - J. Galli (Brescia, Italy)

11h45 **O4** - Encéphalite aigue chez l'enfant: aspects cliniques et follow-up, pattern EEG,  
profils LCR, phénotypes IRM - S-M. Bova (Milano, Italy)

12h00 **O5** - The importance of dealing with treatable conditions. Is it possible for  
a neuropsychiatrist to show no interest in ADHD ? - J. Lopez Pison (Zaragoza, Spain)

12h15 **O6** - Preliminary study of High Density EEG in children and adolescents affected by  
ADHD - E. Buzzzi (Milano, Italy)

12h30 Déjeuner / Lunch

## Vendredi 24 Mars / Friday March 24<sup>th</sup>

### ► Conférences / Lectures

Modérateurs / Moderators : P. Veggiotti, P. Vigiiano

- 13h30** Encéphalites auto immunes causées par des anticorps anti- neuronaux: approche diagnostique / Autoimmune encephalitis due to neural antibodies: diagnosis approach  
C. Bien (Bielefeld, Germany)
- 14h00** Encéphalites auto immunes causées par des anticorps anti-neuronaux: approche thérapeutique / Autoimmune encephalitis due to neural antibodies: therapeutic approach  
T. Granata (Milano, Italy)
- 14h30** Le rôle des anticorps anti-MOG dans les maladies démyélinisantes inflammatoires aiguës : l'exemple de l'ADEM et de la sclérose en plaques  
Role of anti-MOG antibodies in acute demyelinating inflammatory disorders: the example of ADEM and childhood multiple sclerosis  
K. Deiva (Paris, France)
- 15h00** Pathologies neurologiques aiguës dans un contexte d'autoimmunité  
Acute neurological pathologies in an autoimmune context  
V. Leuzzi (Rome, Italy)
- 15h30** Pause / Coffee break

### ► Communications orales / Oral communications

Modérateurs / Moderators : V. San Antonio Arce, A. Arzimanoglou

- 16h00** **O7** - Elucidating the phenotype and the molecular basis of TSC patients with no mutation identified in TSC1 and TSC2 - MP. Canevini (Milano, Italy)
- 16h15** **O8** - Action Observation Treatment in children with cerebral palsy: a combined clinical and functional MRI activation study - A. Molinaro (Brescia, Italy)

### ► Conférence / Lecture

- 16h30** Troubles neurologiques associés aux lésions striatales : classification et approche diagnostique / Neurological disorders associated with striatal lesions: classification and diagnostic approach  
D. Tonduti (Milano, Italy)
- 17h00** Projets de recherche / Research projects  
Modérateurs / Moderators : E. Fazzi, A. Bernabe Gelot
- 18h00** Assemblée Générale de la SENP / SENP General Assembly
- 19h30** Visite culturelle et Dîner du congrès / Cultural visit and congress dinner



## Samedi 25 Mars / Saturday March 25<sup>th</sup>

- 08h00** Meet the experts (Epilepsie)  
Treatment of Drug Resistant Epilepsy  
I. Bagnasco (Torino, Italy) , V. San Antonio (Barcelona, Spain), A. Arzimanoglou (Lyon, France), G. Gobbi (Bologna, Italy), C. Korff (Geneve, Switzerland), P. Veggiotti (Pavia, Italy)

### ► Discussion de dossiers cliniques / Clinical cases discussion

Modérateurs / Moderators : C. Korff, M-L. Moutard

- 09h00** | **DDC1** - A rare cause of intracranial hypertension - G.Perucca (Torino, Italy)
- 09h18** | **DDC2** - The contribution of numerical cognition assessment in differential diagnosis between visuo-spatial versus executive disorder in child with developmental coordination disorder - S. Gonzalez-Monge (Bron, France)
- 09h36** | **DDC3** - Seizures symptomatic of a calcified lesion. Diagnostic and therapeutic approach - P. Costa (Trieste, Italy)
- 09h54** | **DDC4** - A complicated and puzzling course of a cryptogenic epilepsy: a neurodevelopmental disorder or a neurodegenerative disease ? - C. Zanus (Trieste, Italy)
- 10h12** | **DDC5** - Coma néonatal d'installation rapide / Sudden onset neonatal coma  
A. Bernabe Gelot (Paris, France)
- 10h30** | Pause / Coffee break

### ► Pathologies des noyaux gris / Basal ganglia disorders

Modérateurs / Moderators : B. Echenne, D. Doummar

- 11h00** | Diagnostiquer la dystonie à l'ère du séquençage nouvelle génération  
Diagnostics of dystonia in the Next Generation Sequencing era  
G. Collot - Bérout (Marseille, France)
- 11h30** | Mouvements anormaux dans les maladies métaboliques traitables  
Abnormal movements in treatable metabolic diseases  
B. Perez Duenas (Barcelone, Spain)
- 12h00** | Visite des posters / Posters visit
- 13h00** | Déjeuner / Lunch

### ► Conférences / Lectures

Modérateurs / Moderators : A. Roubertie, B. Perez Duenas

- 14h00** | Dyskinésies paroxystiques: an update / Paroxysmal dyskinesia: an update  
D. Doummar (Paris, France)
- 14h45** | Un patchwork des dernières avancées concernant la pathologie des noyaux gris chez l'enfant / Update about recent progress in basal ganglia disorders in children  
A. Roubertie (Montpellier, France)
- 15h30** | Pause / Coffee break

## Samedi 25 Mars / Saturday March 25<sup>th</sup>

### ► Communications orales / Oral communications

Modérateurs / Moderators : P Leroy, J. Fluss

- 16h00** | **O9** - Early-onset ATP1A3 related disorders: clinical description and video presentation of 7 genetically confirmed patients  
E. De Grandis (Genova, Italy)
- 16h15** | **O10** - Hémisphérotomie au dessous de 9 mois chez le nourrisson atteint d'épilepsie réfractaire - V. San Antonio Arce (Barcelona, Spain)
- 16h30** | **O11** - A novel maternally inherited deletion of shank3 causes intellectual disability and unidentified bright objects (ubos)-like brain lesions on cerebral magnetic resonance imaging - G. Terrone (Naples, Italy)
- 16h45** | **O13** - A triad of infantile spasm, binocular nystagmus and focal tonic seizure  
C. Korff (Geneva, Switzerland)
- 17h00** | **O14** - Dystonie de type 11 à début précoce - P. Leroy (Liège, Belgium)
- 17h15** | **O15** - Acute unilateral ophthalmoparesis associated with anti-GQ1b and GM1 antibodies after Parvovirus infection in a 10-year-old girl - C. Canavese (Torino, Italy)
- 17h30** | **O16** - Gradual brain involvement in fetal TSC - A. Bernabe Gelot (Paris, France)
- 17h45** | Remise Prix meilleur poster et meilleure communication  
Award best poster and best oral communication

Les abstracts sont disponibles  
sur le site :

<http://www.senp-neuropediatrie.eu>

**P1 CENTRAL NERVOUS SYSTEM (CNS) DEMYELINATING DISEASES IN CHILDHOOD: A REPORT OF 14 CASES**

M.C. Giraudo (1), C. Canavese (1), C. Brusa (1), S. Mancini (1), A. Tocchet (1), B. Vitiello (1)

(1) *Child and Adolescent Neurology and Psychiatry - University of Turin, Medical School - Città della Salute e della Scienza Hospital, Turin, Italy*

**P2 FLUCTUATING PTOSIS AND GENERALIZED WEAKNESS ASSOCIATED WITH PSEUDO-INTERNUCLEAR OPHTHALMOPLEGIA AND VERTICAL MISALIGNMENT IN A CHILD: A CASE OF JUVENILE MYASTHENIA GRAVIS**

F. Ricci (1), M. Agostini (1), C. Brusa (1), R. Calzetta (1), C. Canavese (1), P. La Rosa (1), B. Vitiello (1)

(1) *Regina Margherita Children Hospital, Turin, Italy*

**P3 PSYCHOMOTOR SLOWING AS THE EMERGING SYMPTOM OF MILD ENCEPHALOPATHY WITH REVERSIBLE SPLENIAL LESION (MERS): A CASE REPORT**

S. Mancini (1), C. Canavese (1), A. Tocchet (1), A. Marone (3), Maria Vittoria De Vita (2), C. Gabbiano (2), P. A. Tovo (2), B. Vitiello (1)

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(2) *Città della Salute e della Scienza Hospital - Paediatric Infectious Diseases Division, University of Turin, Italy.*

(3) *Città della Salute e della Scienza Hospital - Rehabilitation Service of Child and Adolescent Neurology and Psychiatry Division, University of Turin, Italy.*

**P4 INTRAOPERATIVE SEIZURES OCCURRENCE DURING BRAIN MAPPING TECHNIQUES FOR ELOQUENT AREA TUMORS SURGERY: DATA FROM A PEDIATRIC NEUROSURGICAL CENTRE**

F. Ricci (1), C. Brusa (1), C. Carlino (1), P. Costa (2), P. Gagliani (1), M. Giacobbi (1), A. Palmitezza (1), P. Ragazzi (1), P. Peretta (1)

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**P5 GLUT1 DS: THE COGNITIVE ASPECTS**

C. Varesio (1,2), V. De Giorgis (1,2), S. Masnada (1,2), M. Alessio Chiappedi (1), M. Zanaboni (1), M. Filippini (3), S. Donetti Dantin (1,2), J. Ann Macasaet (4), U. Balottin (1,2), P. Veggiotti (1,2)

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(4) *Department of Neurosciences, Makati Medical Center, Manila, Philippines*

**P6 PAEDIATRIC GLIOMATOSIS CEREBRI: CLINICAL PRESENTATION, PROGNOSTIC FACTORS AND APPROPRIATE MANAGEMENT**

G. Prato (1), M.M. Mancardi (1), G. Morana (1), Alessandro Consoles (1), Paolo Nozza (1), Maria Giuseppina Baglietto (1), Maria Luisa Garrè (1), Edvige Veneselli (1)

(1) *Giannina Gaslini Children's Hospital, Genoa, Italy*

**P7 AICARDI-GOUTIÈRES AND SINGLETON-MERTEN SYNDROMES: AN OVERLAPPING PHENOTYPE ASSOCIATED WITH A GAIN-OF-FUNCTION MUTATION IN IFIH1**

V. De Giorgis (1, 2), M. De Simone (3), J. Galli (3,4), M. Cattalini (4, 5), D. Tonduti (6), M. Estienne (6), B. Garavaglia (7), C. Cereda (8), D. Sproviero (8), A. Pichiecchio (9), L. Chiapparini (10), G. Rice (11), Y.J. Crow (12) E. Fazzi (3, 4), S. Orcesi (1)

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## **P8 CYCLIC VOMITING IN PATIENT WITH NEUROFIBROMATOSIS**

S. Masnada PhD MD (1,2), S. Esposito MD (3), V. Saletti MD (3), U. Balotini MD (1,2), A. Pichiecchio MD (4), M. Delmonte MD (5), P. Veggiotti MD (1,2), S. Orcesi MD (2)

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(5) Radiology Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.

## **P9 POST-VARICELLA ANGIOPATHY: A FREQUENT BUT UNDERESTIMATED CAUSE OF INFANTILE STROKE WITH GOOD PROGNOSIS**

G.Gattuso (1), SM.Bova (2), G.Bernardi (3), G.Izzo (4), D.Dilillo (1), G.Zuin (1), M.Mastrangelo (2), GV.Zuccotti (1)

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## **P10 DRAMATIC RELAPSE OF SEIZURES AFTER EVEROLIMUS WITHDRAWAL**

A.Mingarelli (1), A.Vignoli (1,2), A.Peron (1,2), F.La Briola (1), MN.Savini (1), L.Giordano (3), MP.Canevini (1,2)

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(2) Department of Health Sciences, Università degli Studi, Milan, Italy

(3) Paediatric Neuropsychiatric Division, Spedali Civili, Brescia, Italy

## **P11 NOUVELLE MUTATION DU GÈNE CCDC22 RESPONSABLE D'UN SYNDROME DE DANDY WALKER SYNDROMIQUE, LIÉ À L'X**

S. Valence (1,2,3,4), D. Doummar (1,2,3), E. Lacaze (2), M. Montchilova (5), C. Garel (2,3,6), S. Puget (7), S. Chanto Bastaraud (2,3,8), L. Burglen (2,3,4,8), D. Rodriguez (1,2,3,4)

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(7) CHU Necker Enfant Malade, service de Neurochirurgie, Paris, FR

(8) APHP, GHUEP, Hôpital Trousseau, Genetic, Paris, FR

## **P12 MAUVAISE TOLÉRANCE À L'INTRODUCTION D'UN RÉGIME CÉTOGÈNE POUR SUSPICION DE DÉFICIT EN PDH : ÉVOQUONS UN AUTRE DIAGNOSTIC ?**

M.C. Nougues (1), A. Guët (2), M. Fazzio (3), N. Danekova (2), S. Valence (1), T. Billette de Villemeur (1), C.Garel (4), D. Rodriguez (1), A. Boutron (5)

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(4) Service de Radiopédiatrie, CHU Armand Trousseau, APHP, Paris

(5) Biochimie, CHU Kremlin Bicêtre, APHP, Le Kremlin Bicêtre

## **P13 PHENOTYPIC AND GENOTYPIC FEATURES OF A POPULATION OF PATIENTS WITH AUTISM SPECTRUM DISORDERS**

V. Tessarollo (1,2), E. Magnaghi (1,2), M. Saccani (1), A. Peron (1,3), P. Olgiati (1), A. Vignoli (1,2), M.P. Canevini (1,2)

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(2) State University of Milan, Milan, Italy

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The 45<sup>th</sup> meeting of the European Society of Pediatric Neurology (Société Européenne de Neurologie Pédiatrique) to be held in Torino, Italy (23.–25.03.2017) was granted 15 European CME credits (ECMEC) by the European Accreditation Council for Continuing Medical Education (EACCME).

European Accreditation is granted by the EACCME in order to allow participants who attend the above-mentioned activity to validate their credits in their own country.

### Accreditation Statement

« The 'Société Européenne de Neurologie Pédiatrique' (or) '45<sup>th</sup> meeting of the European Society of Pediatric Neurology (Société Européenne de Neurologie Pédiatrique)' is accredited by the European Accreditation Council for Continuing Medical Education (EACCME) to provide the following CME activity for medical specialists. The EACCME is an institution of the European Union of Medical Specialists (UEMS), [www.uems.net](http://www.uems.net). »

« The '45<sup>th</sup> meeting of the European Society of Pediatric Neurology (Société Européenne de Neurologie Pédiatrique)' is designated for a maximum of (or 'for up to') 15 hours of European external CME credits.

Each medical specialist should claim only those hours of credit that he/she actually spent in the educational activity. »

« Through an agreement between the European Union of Medical Specialists and the American Medical Association, physicians may convert EACCME credits to an equivalent number of AMA PRA Category 1 Credits™.

Information on the process to convert EACCME credit to AMA credit can be found at [www.ama-assn.org/go/internationalcme](http://www.ama-assn.org/go/internationalcme). »

« Live educational activities, occurring outside of Canada, recognized by the UEMS-EACCME for ECMEC credits are deemed to be Accredited Group Learning Activities (Section 1) as defined by the Maintenance of Certification Program of The Royal College of Physicians and Surgeons of Canada. »

### EACCME credits

Each medical specialist should claim only those hours of credit that he/she actually spent in the educational activity.

An evaluation form will be distributed onsite, you will need to return it to the registration desk in order to claim your CME credits.

## C.M.E



**European Union of Medical Specialists**  
EACCME - European Accreditation Council for Continuing Medical Education  
Institution of the UEMS  
Rue de Dintelste 24, B-1200 Brussels  
T: +32 2 549 5164 | F: +32 2 549 37 30 | E: accreditation@uemss.eu

Société Européenne de Neuro-pédiatrie

**SUBJECT: EACCME accreditation granted EACCME 16642-G**

We are pleased to inform you that your application for European accreditation for:

**SENP 2017 Congress**

Venue: (Venice, Italy (23-25/03/2017))

(Event code: 15042)

was granted 15 European CME credits (EACCME) by the European Accreditation Council for Continuing Medical Education (EACCME).

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Accreditation by the EACCME system through its participating accreditation statement communication materials including the registration address the event is guaranteed at the official accreditation. The following statements must be accepted/confirmed:

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**Feedback report:**

The EACCME accreditation project a feedback report is provided after each event completed together with a copy of the list of participants and the results of individual feedback assessments by participants.

Brussels, 3<sup>rd</sup> 2017. The UEMS / EACCME Secretariat

EACCME is an acronym for European Accreditation Council for Continuing Medical Education.

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## INSCRIPTION / Registration

En ligne sur / Online: [www.senp-neuropediatrie.eu](http://www.senp-neuropediatrie.eu)

### TARIFS INSCRIPTION / REGISTRATION FEES

	Avant le 10/03/17	Après le 10/03/17
MEDECIN MEMBRE SENP/SINP Member registration fee	350 €	435 € €
MEDECIN NON MEMBRE SENP/SINP Non member registration fee	425 €	510 € €
MEDECIN FORMATION Education registration fee	250 €	300 € €
INSCRIPTION AU COURS Course registration fee	80 €	80 € €
INSCRIPTION DÎNER ET EXCURSION Site visit and dinner registration fee	65 €	65 €

## VISITE CULTURELLE ET DÎNER DU CONGRÈS Cultural visit and congress dinner



Le dîner du congrès se déroulera le **vendredi 24 mars 2017** à 20h30 au Restaurant La Smarrita, à Turin.

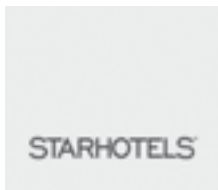
Départ à 19h30 du lieu du congrès. Une visite culturelle précèdera le dîner.

The congress dinner will take place at the Restaurant La Smarrita of Turin, March 24th, 2017 at 8.30 pm.

Departure will be at 7.30 p.m from the conference venue. A cultural visit will take place before dinner.

Inscriptions sur / Registration on:  
[www.senp-neuropediatrie.eu](http://www.senp-neuropediatrie.eu)

## ACCES / Congress venue



### STARHOTELS MAJESTIC TORINO

Corso Vittorio Emanuele II, 54

10123 Torino, Italia

T: +39 011 539153

<http://www.starhotels.com/it>

### ACCES AU LIEU DU CONGRES

► **De la gare :**

100m de la Gare ferroviaire Porta Nuova.

► **De l'autoroute :**

De l'autoroute A4 Torino / Venezia et de l'autoroute A5 Aosta / Torino (7 km), sortir Corso Giulio Cesare et aller en direction du centre ville / gare Porta Nuova.

De l'autoroute A6 Savona / Torino et l'autoroute A21 Piacenza / Torino (5 km), sortir Corso Unità d'Italia et poursuivre en direction du centre ville / gare Porta Nuova.

De l'autoroute A32 Bardonecchia / Torino (6km), sortir à Corso Francia et poursuivre en direction du centre ville / gare Porta Nuova.

Il n'y a pas de parking à l'hôtel.

► **De l'aéroport :**

De l'aéroport de Caselle «Sandro Pertini» (27km), prendre le bus de la gare vers le centre ville et descendre à la gare Porta Nuova.

### HOW TO GET TO THE CONFERENCE VENUE

► **By train :**

The train station is located at 5 min from Porta Nuova station.

► **By car :**

A4 Torino / Venezia and A5 Aosta / Torino (7 km) freeways - Exit: Corso Giulio Cesare and follow signs to town center / Porta Nuova station.

A6 Savona / Torino and A21 Piacenza / Torino (5 km) freeways - Exit: Corso Unità d'Italia and follow signs to town center / Porta Nuova station.

A32 Bardonecchia / Torino (6km) freeways - Exit: Corso Francia and follow signs to town center / Porta Nuova station.

There is no car park at the hotel.

► **By plane :**

From the Caselle «Sandro Pertini» airport (27km), you can take a shuttle bus to the town center - Exit: Porta Nuova Station.



## **ACCUEIL DU CONGRÈS / CONGRESS REGISTRATION DESK**

Horaires d'ouverture / Opening hours

<b>Jeudi 23 mars</b> 12h30 à 19h30	<b>Vendredi 24 mars</b> 07h30 à 18h30	<b>Samedi 25 mars</b> 07h30 à 18h30
Thursday, March 23 <sup>rd</sup> 12:30 p.m to 7:30 p.m	Friday, March 24 <sup>th</sup> 7:30 a.m to 6:30 p.m	Saturday, March 25 <sup>th</sup> 7:30 a.m to 6:30 p.m

## **Restauration / Catering**

Apéritif de bienvenue pour les inscrits au congrès SENP  
(exceptés les inscrits aux cours) le jeudi 23 mars à 20h.

Welcome cocktail reception for SENP congress attendees (except those attending only the SENP classes) Thursday, March 23<sup>th</sup> at 8 p.m.

Les déjeuners se dérouleront dans la salle des petits déjeuners de l'hôtel.

Les desserts et les pauses seront servis sur l'espace d'exposition.

Lunches will take place in the Hotel's breakfast room. Desserts and coffee breaks will take place in the exhibit hall.

## **Posters**

Dimensions : hauteur 1 m / largeur 0.90 m.

Le matériel de fixation du poster sera remis à l'accueil.

Dimensions : height 1.10m / width : 0.90m

Fixing supplies will be handed out to you onsite at the congress secretariat.

Affichage : Jeudi 23 mars avant 15h00

Retrait : Samedi 25 mars au plus tard à 18h30

(aucun poster ne sera gardé après)

Posters set-up : Thursday, March 23<sup>th</sup> before 3.00 p.m

Posters take-out : Saturday, March 25<sup>st</sup> at 6.30 p.m at the latest  
(no posters will be kept after that time)

# ▶ **RESUMES** ◀

## **ABSTRACTS**

p.19	Communications orales	Oral communications
p.33	Dossiers cas cliniques	Clinical cases
p.38	Posters	
p.51	Conférences	

## ENCEPHALOPATHIES WITH INTRACRANIAL CALCIFICATIONS IN CHILDREN: MOLECULAR AND PHENOTYPIC CHARACTERIZATION FROM MULTICENTRIC SERIES

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(3) Child Neurology and Psychiatry Unit, Foundation IRCCS C. Mondino Neurological Institute, Pavia, Italy

(4) Department of Neuroradiology, Foundation IRCCS C. Besta Neurological Institute, Milan, Italy

(5) Department of Neuroradiology, C. Mondino National Neurological Institute, Pavia, Italy

(6) Department of Translational Medicine, University of Milan Bicocca, Milan, Italy

**BACKGROUND AND AIM OF THE STUDY:** several genetic encephalopathies with pediatric onset are characterized by the presence of cerebral calcification, such as Aicardi-Goutières syndrome, Cockayne syndrome, Krabbe disease. Collectively they constitute a group of disabling neurological disorders with variable age at onset and heterogeneous clinical presentations. Our aim was to analyze a series of pediatric patients with evidence of intracranial calcification by a customized gene panel through Nextera Rapid Capture Custom Enrichment.

**METHODS:** we collected clinical and radiological data from patients affected by a pediatric onset encephalopathy of unknown cause characterized by the presence of cerebral calcification documented on at least one CT scan. Inclusion criteria encompassed also the presence of at least one MRI, negativity for congenital infections, calcium, phosphate, and parathyroid hormone metabolism abnormalities, genetic analyses performed for diagnostic purposes. DNA samples were tested by Nextera Rapid Capture Custom Enrichment (MiSeq Illumina platform). We used customized gene panels including 64 genes associated with known genetic diseases with cerebral calcification.

**RESULTS:** We collected a series of 47 patients. All patients displayed complex and heterogeneous phenotypes often including psychomotor retardation and pyramidal signs and less frequently movement disorder and epilepsy. Signs of cerebellar and peripheral nerve system involvement were occasionally present. The most frequent MRI abnormality was the presence of white matter involvement; calcifications were localized in basal ganglia and cerebral white matter in the majority of cases. 20/47 (42%) patients tested positive for mutations in one of the 64 genes analyzed. In 14/20 the analysis lead to a definite genetic diagnosis (8 AGS2, 1 RNASET2, 1 ERCC6, 1 ERCC8, 1 COL4A1, 1 CYP2U1) while in the other 6/20 results were controversial.

**CONCLUSIONS:** Genetic encephalopathies with cerebral calcification are usually associated to complex phenotypes. NGS is a powerful instrument to widen the clinical spectrum of genes associated with cerebral calcifications. In our series, a molecular diagnosis was achieved in 30% of cases, suggesting that the molecular basis of a large number of genetic encephalopathies with cerebral calcification is still to be elucidated. This confirms also that deep phenotyping is still very helpful and particularly the presence of cerebral calcification is a good criteria to collect homogeneous groups of patients to be studied by exome or whole genome sequencing.

## EXPLORING AUTOIMMUNITY IN A COHORT OF CHILDREN WITH AICARDI-GOUTIÈRES SYNDROME

Jessica Galli (1,2), Marco Cattalini (2,3), Laura Andreoli (2,4), Ivana Olivieri (5,6), Giada Ariaudo (5), Micaela Fredi (4), IAGSA study group (F. Bettera, M. Bianchi, N. Carabellese, M. De Simone, R. Ferraro, F. Gavazzi, S. Giliani, G. Gualdi, A. Meini, I. Parissenti, D. Vairo, A. Zanola, C. Cereda), Simona Orcesi (5), Angela Tincani (2,4), Elisa Fazzi (1,2)

- (1) Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
- (2) Child Neurology and Psychiatry Unit, ASST Civil Hospital, Brescia, Italy
- (3) Pediatric Clinic, Spedali Civili di Brescia, Brescia, Italy
- (4) Department of Clinical Immunology and Rheumatology, ASST Civili Hospital, Brescia, Italy
- (5) Child Neurology and Psychiatry Unit, C. Mondino National Neurological Institute, Pavia, Italy
- (6) Don Carlo Gnocchi ONLUS Foundation, Milan, Italy

**Study objectives:** Aicardi–Goutières syndrome (AGS) is a rare genetic inflammatory encephalopathy arising during the first year of life. Phenotype is characterized by neurological manifestations, increased cerebrospinal fluid interferon-alpha levels and cardinal neuroradiologic features (intracranial calcifications, leucodystrophy and cortical atrophy).

Extraneurological symptoms evocative of autoimmunity are described, too. To date the real impact of autoimmunity in these patients is still debated. The aim of our study is to explore the eventual presence of autoimmune manifestations and characterize the autoantibody profile in a cohort of subjects with AGS.

**Methods:** seventeen children with genetically-confirmed diagnosis of AGS were enrolled. Past medical and family history was reviewed, looking for signs or symptoms of autoimmune disorders. Accurate neurological examination and evaluation of the motor functions, manual abilities and communication competence were also performed. The following autoantibodies were measured in AGS patients' blood samples: anti-nuclear, anti-doublestranded-DNA, anti-nucleosome, anti-extractable nuclear antigens, anti-cardiolipin IgG/IgM, anti-glycoprotein I IgG/IgM, and anti-neutrophil cytoplasmic. Complement levels (C3, C4 and CH50) were measured, too.

**Main Results:** nine out of seventeen patients had at least one first- or second-degree relative with a history of autoimmune diseases (children's mother or grand-mother in the majority of cases). A specific autoimmune disease was present in one AGS patient, namely an autoimmune thyroiditis.

Nine subjects showed abnormal autoantibodies profile with different patterns of positivity, while all the patients presented normal levels of complement. No correlation between auto-antibody production and personal or family history of autoimmune diseases was found.

**Conclusions:** specific autoimmune diseases are not common in patients with AGS. Autoantibodies, mainly directed towards nucleic acids-containing elements, seem not to be pathogenic rather representing an epiphenomenon of enhanced interferon production. The presence of autoantibodies seems to be a characteristic of type I interferonopathies that links this disease with systemic lupus erythematosus, considered itself an interferon-alfa dependent disease too.

Drugs targeted to limit the effects of interferon dysregulation rather than classic immunosuppressants should be considered as a possible treatment for AGS.

## ENCEPHALITE AIGUE CHEZ L'ENFANT: ASPECTS CLINIQUES ET FOLLOW-UP, PATTERN EEG, PROFILS LCR, PHENOTYPES IRM

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(2) Laboratoire de Pathologie Clinique et Génétique, Fondazione IRCCS Istituto Neurologico C Besta, Milano, Italia;

(3) Service de Radiologie et Neuroradiologie Pédiatrique ASST Fatebenefratelli Sacco, Ospedale dei Bambini V Buzzi, Milano, Italia,

(4) Service di Pédiatrie, ASST Fatebenefratelli Sacco, Ospedale dei Bambini V Buzzi, Milano Italia

### Le but du travail :

L'encéphalite aiguë est une pathologie inflammatoire du SNC sévère et invalidante. Parmi les encéphalites liées aux infections qui se présentent au cours ou au décours d'un épisode viral le plus souvent, on distingue les encéphalites infectieuses par agression directe du pathogène des encéphalites dites post-infectieuses liées à un mécanisme immunologique. Plus récemment ont été décrites des formes autoimmunes liées à la présence d'autoanticorps et markers biologiques spécifiques. Le diagnostic différentiel est complexe, et l'agent étiologique reste inconnu dans de nombreux cas. Pour mieux caractériser les tableaux cliniques des encéphalites de l'enfant nous avons fait une analyse rétrospective des cas pris en charge dans le Service de Neurologie Pédiatrique entre janvier 2006 et décembre 2016.

La méthodologie L'étude porte sur une série de 25 enfants (age moyen 4 ans, range six mois-9 ans) avec une diagnostique de encéphalite aiguë (Vinkatesan, 2013). La présentation clinique, la composition du liquide céphalorachidien, l'électroencéphalogramme, l'IRM, et l'évolution ont été analysés.

### Les résultats principaux obtenus :

L'agent causal a été déterminé 12 fois (48%): virus herpétiques chez dix enfants (40 %), et entérovirus chez deux (8 %).

Quinze enfants (60 %) avaient une histoire infectieuse, vingt (80%) de la fièvre. Vingt quatre avaient une altération de la vigilance.

Douze (48 %) ont présenté des convulsions focales, dont deux avec état de mal. Onze (44 %) avaient un trouble de l'équilibre, six (24%) une hémiparésie et des signes pyramidaux, cinq (20%) des troubles du comportement; deux enfants avec myélite avaient un paralysie flasque; cinq (20 %) un syndrome méningé. Le LCR (réaction cellulaire, protéinorachie, glycorachie) était altéré chez onze enfants (44%), la PCR était positive chez trois. Une synthèse intrathécale d'immunoglobulines (IgG ou IgM ou chaînes légère libres) a été documentée chez dix enfants. Un ralentissement diffus (thêta, thêta-delta, delta) ou focal de l'EEG était présent chez tous dès le premier tracé. L'IRM a documenté des altérations au niveau du cortex et de la substance blanche hémisphérique (28%), des noyaux gris centraux (28 %), et plus rarement du corps calleux, des structures limbiques, du tronc, du cervelet et de la moelle.

### Les conclusions :

L'aspect le plus important est l'hétérogénéité des tableaux cliniques et neuroradiologiques et l'homogénéité des altérations EEG qui sont liées à l'encéphalopathie, mais aspécifiques. L'agent étiologique reste inconnu dans la moitié des cas, mais l'évidence d'une synthèse intrathécale d'immunoglobulines et l'histoire clinique peut faire penser à une origine infectieuse.

L'évolution à long terme est favorable chez la plupart des enfants, indépendamment de la gravité du tableau clinique. La corrélation entre données cliniques, IRM et EEG avec l'agent étiologique est faible.

## THE IMPORTANCE OF DEALING WITH TREATABLE CONDITIONS. IS IT POSSIBLE FOR A NEUROPEDIATRICIAN TO SHOW NO INTEREST IN ADHD?

Javier López Pisón (1), Silvia, Sánchez Marco (1), Cristina Fuertes Rodrigo (1), Ruth Rodrigo Martínez (1), Miguel Lafuente Hidalgo (1), Lorena Monge Galindo (1), Jose Luis Peña Segura (1)

(1) Sección neuropediatría Hospital Miguel Servet. Zaragoza

### Introduction:

Attention deficit hyperactivity disorder (ADHD) is the most prevalent neurodevelopmental disorder, and the only one with effective treatment of its nuclear symptomatology. In the general population, the prevalence is about 3-7% of school-age children and 2-5% of adults. It can be isolated or associated to other neurodevelopmental disorders such as intellectual disability, autism spectrum disorder and learning disorders, and to various cerebral problems. The cases of children over six years old that were attended at the neuropediatrician unit during a 13-month period are reviewed here, and the cases with ADHD are analyzed.

### Results:

Between september 2015 and october 2016, 2406 children born before the 31-08-10 were attended, 948 with ADHD: 39,4% of the school-age children that were followed at the neuropediatrician unit. They were diagnosed as ADHD, 38,8% of the children that were evaluated at any time because of developmental delay (65/426 born before 31-8-10). They were listed as ADHD, 48,8% (19 out of 39) of the school-age children affected by neurofibromatosis 1, 16,1% (38/236) by cerebral palsy, 30% (3/10) by tuberous sclerosis, 61,8% (92/149) by tics. 25,11% (108/430) of the school-age epileptic children had ADHD.

### Discussion:

ADHD is frequently associated with other problems not analyzed here such as cerebral tumours. Our data are similar to those referred to in the literature. ADHD is common in a great number of children managed at neuropediatric units, and we are responsible for its early identification and correct treatment, under the very important premise for neuropediatricians: "to treat the treatable".

## PRELIMINARY STUDY OF HIGH DENSITY EEG IN CHILDREN AND ADOLESCENTS AFFECTED BY ADHD

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(1) Child and Adolescence Neuropsychiatric Unit, ASST Santi Paolo e Carlo Milano, Italy

(2) Psychiatric Unit, ASST Santi Paolo e Carlo Milano, Italy

### Study Objectives:

Although ADHD is classified as a neurodevelopmental disorder, the use of biomarkers isn't currently recommended in the diagnosis and follow up. Finding distinctive patterns of EEG abnormalities with more advanced techniques that could increase specificity and spatial location, could pave the way to the development of more personalized intervention strategies and more sensitive diagnostic procedures and specifications. The present study employs the high density EEG ( HD - EEG ) that uses a greater number of electrodes to overcome the space limitations of the standard EEG scalp and the high density electrodes to increase spatial precision.

Objective of the study is identification of possible biomarkers of ADHD and possible correlations with neuropsychological and behavioral profiles.

### Materials and Methods:

6 ADHD patients (diagnosed according to DSM-5 criteria) have been recruited: 5 males and 1 female. Mean age was 12 years and 6 months. A control population of 5 healthy subjects has been recruited ( 4 females and 1 male , mean age: 12 years 8 months). Subjects have compiled the following questionnaires: Child Behavior Checklist 6-18 (CBCL 6-18), CBCL-Youth Self Report, Conner's Parent Rating Scale-revised (CPRS-R). Each participant had High Density EEG recording (64 electrodes) in a state of rest and during administration of the Conners Continuous Performance Test 3rd Edition ( Conners CPT3)

### Main Results:

An augmented Theta/Beta Ratio(TBR) was significantly ( $p < 0,05$ ) more expressed in subjects with ADHD than controls and we assume that TBR could be a valid biomarker of disease.

By using HD-EEG it was possible to better localize brain areas where Theta/Beta ratio was significantly increased compared to healthy controls (areas:C3; P3; P4; Cz; CP1 CP2; C1; P1; P2; CP3; CP4; CPZ; POZ) . Cortical areas involved were medium-parietal, with a little predominance of the right hemisphere.

Increasing TBR correlated with worse attentional performance at the CPT, especially sustained attention. No significant correlations were observed regarding variables related to symptomatological clusters like Impulsivity and Vigilance.

Concerning CBCL and CBCL-YSR we appreciated a correlation between augmented ratio theta / beta and internalizing symptoms. The correlation for questionnaires indexes affected only some of the 13 selected electrodes , in particular C1 , Cz , C3 .

### Conclusion:

In our patient population an augmented TBR in the central and parietal areas could be considered as valid biomarker of disease. It has been observed to correlate with internalizing symptoms (from questionnaires) and deficits in attention detected with CPT3. Sustained attention deficit correlated with altered values in the TBR more than controls. Limitation of this study is the low sample size and lack of proportion between males and females . The results are to be considered very preliminary . We intend to continue in the future with the study to expand the sample and have the opportunity to confirm these preliminary results .

## ELUCIDATING THE PHENOTYPE AND THE MOLECULAR BASIS OF TSC PATIENTS WITH NO MUTATION IDENTIFIED IN TSC1 AND TSC2

A.Vignoli (1), A.Peron (1,2), B.Moore (3), F.La Briola (1), V.Chiesa (1), A.Mingarelli (1), R.M.Alfano (4), D.Viskochil (2), J.C.Carey (2), M.P.Canevini (1), on behalf of the TSC Study Group of the Santi Paolo-Carlo University Hospital (Milan, Italy)

(1) Child Neuropsychiatry Unit - Epilepsy Center, Santi Paolo-Carlo Hospital, Department of Health Sciences, Università degli Studi, Milan, Italy

(2) Department of Pediatrics, Division of Medical Genetics, University of Utah School of Medicine, Salt Lake City, UT, USA

(3) Department of Human Genetics, University of Utah, Salt Lake City, UT, USA

(4) Human Pathology Unit, Santi Paolo-Carlo Hospital, Department of Health Sciences, Università degli Studi, Milan, Italy

Tuberous Sclerosis Complex (TSC) is caused by mutations in TSC1 or TSC2. No mutation is identified (NMI) in 10-15% of patients with a clinical diagnosis, despite full conventional molecular assessment. We performed a detailed clinical evaluation of 22 NMI individuals with a definite clinical diagnosis of TSC, and looked for the genetic cause in these patients by means of Whole Genome Sequencing (WGS).

NMI individuals had a median age at diagnosis of 18 yrs (0-50 yrs). One patient had intellectual disability (ID) and 7 (31.82%) showed TSC-associated neuropsychiatric disorders (TAND) other than ID and autism. When compared to 65 patients with a mutation in TSC1, NMI individuals were more often simplex cases ( $p=0.001$ ), had more frequent renal angiomyolipomas ( $p=0.001$ ), especially larger than 3 cm ( $p=0.003$ ), and more pulmonary manifestations ( $p=0.001$ ). When compared to 125 patients with a mutation in TSC2, NMI individuals were diagnosed at an older age ( $p=0.001$ ), had more frequent normal cognition ( $p<0.001$ ) and less frequent epilepsy and infantile spasms ( $p=0.010$  and  $p=0.012$ ), less frequent subependymal nodules ( $p=0.022$ ) and giant cell astrocytomas ( $p=0.008$ ) without difference in frequency of cortical tubers. Also, cardiac rhabdomyomas were less frequent in NMI patients (27.27% vs 49.14%;  $p=0.066$ ).

Chromosomal microarray (average resolution: 130 kb) in the NMI patients showed no causative microdeletions or microduplications. WGS has been completed in 10 trios, and we are currently analyzing the results. Although WGS is unlikely to detect low level mosaicism due to the relatively low read depth, we identified one mosaic mutation in TSC2 (c.1372C>T, p.Arg458Ter), not present in the parents and known to be pathogenic, with an allele frequency of 1.67%. We also detected an interesting variant in an X-linked gene in another patient, inherited from his healthy mother, and predicted to be deleterious in silico. We are currently evaluating the significance of 3 missense heterozygous variants in two genes encoding peptides in the mTOR pathway. These findings facilitate the delineation of distinctive phenotypes indicative of NMI patients, and, although preliminary, suggest that other genes might be considered when mosaicism or TSC1/TSC2 intronic mutations are not found in these patients.



**ACTION OBSERVATION TREATMENT IN CHILDREN WITH CEREBRAL PALSY:  
A COMBINED CLINICAL AND FUNCTIONAL MRI ACTIVATION STUDY**

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The systematic observation of daily actions followed by their imitation (Action Observation Treatment, AOT) is a novel rehabilitation approach exploiting a well-known neurophysiological mechanism matching an observed action on its motor counterpart through the mirror neuron system. The aim of this randomized controlled trial was to assess whether AOT may improve upper limb motor functions in children with cerebral palsy (CP). 12 children with CP were enrolled and randomly assigned to either an experimental (n=6) or control (n=6) group. The experimental group observed video clips showing daily age-appropriate actions and afterwards imitated the observed actions. The control group observed video clips with no motor content and afterwards executed the same actions as cases. The primary outcome measure was the Assisting Hand Assessment, the Melbourne Assessment Scale and ABILHAND-Kids were secondary ones. Functional Magnetic Resonance Imaging (fMRI) was performed in all subjects with specific stimulation protocols of manipulation of complex-shaped objects. Children were scored twice at baseline (2 wks apart), at the end and 8 weeks after the treatment, by a physician blind to group assignment. After treatment, the functional score gain was significantly different in the case and control groups for both the AHA ( $p=0,004$ ) and the Melbourne ( $p=0,003$ ) assessments; non changes were found for ABILHAND-Kids. In the experimental group, fMRI showed an increase in activations in ventral pre-motor areas after AOT. Using seed regions from the fMRI maps, the DTI analysis with fiber tracking revealed structural connections within the fronto-parietal circuit.

## EARLY-ONSET ATP1A3 RELATED DISORDERS: CLINICAL DESCRIPTION AND VIDEO PRESENTATION OF 7 GENETICALLY CONFIRMED PATIENTS

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### Study objectives:

Mutations in the ATP1A3 gene, which encodes the alpha3-subunit of sodium-potassium ATPase, are related to a phenotypic spectrum including mainly Rapid Onset Dystonia-Parkinsonism (RDP), Alternating Hemiplegia of Childhood (AHC) and Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy, and Sensorineural hearing loss (CAPOS) syndrome. The rarity of these disorders and the broad clinical spectrum make the diagnosis really difficult. We present 7 genetically confirmed patients with the help of video documentation.

### Methods:

Sequencing of the coding region of the ATP1A3 gene showed a de-novo mutation in 7 patients (3 M, 4 F, age range 4 - 30 years) presenting complex paroxysmal and non-paroxysmal movement disorders.

Clinical data have been collected and paroxysmal and non-paroxysmal video documentation have been reviewed.

### Main results obtained:

All the 7 patients presented different de-novo ATP1A3 mutations. Three patients had typical AHC, 1 patient had atypical AHC, 2 patients had atypical RDP phenotype with channelopathy-like spells and finally the last patient presented fever related not remitting ataxia with dyskinetic features. Onset was before 18 months of age. Dystonia of different degree was a common clinical feature, as well as various paroxysmal disturbances.

### Conclusions:

ATP1A3-related disorders make up a complex phenotypical continuum. Paroxysmal manifestations may overlap, since are always present in AHC but, even less frequently, also in other variants phenotypes. ATP1A3 analysis should be considered also in children with channelopathy-like spells and early onset fever-related encephalopathy.

**HEMISPHEROTOMIE AU DESSOUS DE 9 MOIS CHEZ LE NOURRISSON ATTEINT D'ÉPILEPSIE REFRACTAIRE**

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**But du travail:**

Dans les cas d'épilepsie réfractaire de cause structurelle hémisphérique à débuts précoces, l'hémisphérotomie a de bons résultats en termes de contrôle des crises, mais souvent des troubles du développement graves persistent. La réalisation précoce de l'hémisphérotomie pourrait être associée à un risque chirurgical élevé, mais avec un meilleur pronostic cognitif. Le but de ce travail est de décrire notre série de nourrissons atteints d'une épilepsie réfractaire à début précoce ayant eu un hémisphérotomie avant l'âge de 9 mois.

**Méthodologie:**

Des variables cliniques, les complications et l'évolution des 4 patients atteints d'une épilepsie réfractaire à début précoce ayant eu un hémisphérotomie avant l'âge de 9 mois ont été collectées rétrospectivement.

**Résultats:**

Chez 4 patients une hémisphérotomie a été effectuée à 4, 5, 7 et 8 mois. Le début de l'épilepsie était dans les premiers jours de vie dans 3 cas. Dans tous les cas, il existait absence de contrôle des crises et présence de déficits moteurs et retard du développement au moment de l'intervention. Dans tous les cas la cause était une pathologie hémisphérique malformative congénitale. Dans 1 cas il y avait l'hyperthermie postopératoire, dans 2 cas des crises entre 7 et 30 jours après la chirurgie. Le contrôle consécutif des crises était complet dans 3 cas (12m suivi maximal).

Dans tous les cas il y avait une légère aggravation du déficit moteur et une amélioration du développement, bien que dans le cas avec suivi plus prolongé un retard de développement persiste.

**Conclusions:**

Dans notre série de patients l'hémisphérotomie mène au contrôle ou l'amélioration des crises sans complications. La réalisation d'hémisphérotomie précoce dans d'autres cas et le suivi montreront si une amélioration significative des résultats cognitifs est atteinte.

## **A NOVEL MATERNALLY INHERITED DELETION OF SHANK3 CAUSES INTELLECTUAL DISABILITY AND UNIDENTIFIED BRIGHT OBJECTS (UBOS)-LIKE BRAIN LESIONS ON CEREBRAL MAGNETIC RESONANCE IMAGING**

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### **Study objectives:**

Microdeletions of 22q13 region involving SHANK3 gene are responsible for Phelan-McDermid syndrome (PMS) whereas SHANK3 mutations have been reported in patients with autism or intellectual disability (ID). Neurological features of PMS include global developmental delay/ID, speech disorder, autism spectrum disorder and hypotonia. Brain Magnetic Resonance Imaging (MRI) studies detected in PMS patients arachnoid cysts, ventriculomegaly, dysmyelination, morphological changes of the corpus callosum, and cerebellar malformations. So far, no affected individuals with SHANK3 deletion have been known to reproduce. We report a family with four affected individuals including the mother, her male monozygotic twins and her daughter harboring a novel SHANK3 interstitial microdeletion. All four members presented with ID and the twins also showed brain abnormalities similar to Unidentified Bright Objects (UBOs), present in patients with Neurofibromatosis type 1.

### **Methods:**

The mother was born at term after a normal pregnancy. She had low level of school education but she was independent in her daily life activities. At 37 years old, her neurological exam and anthropometric parameters were normal. An evaluation of her cognitive functions by Wechsler Adult Intelligence Scale–Revised (WAIS-R) showed a Full Scale Intelligence Quotient (FSIQ) of 51. Monozygotic male twins were born at term after a normal gestation. Birth weight and Apgar scores were normal. At 10 years old, except for overweight, height and head circumference were normal. An evaluation of cognitive functions by the Wechsler Intelligence Scale for Children (WISC-IV) gave a FSIQ of 43 and 41 in the twin A and B. A language deficit was evident in both twins. Brain MRI showed small FLAIR and T2 hyperintensities located respectively in the left globus pallidus and right thalamus in twin A and in the left cerebral peduncle, both thalami, left globus pallidus, bilateral temporal periventricular white matter in twin B. The 8 year-old daughter was born at term after a gestation complicated by intrauterine growth retardation (IUGR). She had a history of growth retardation and speech delay. At 7 years old, anthropometric parameters were normal. An evaluation of intellectual level, performed by WISC-IV, showed a FSIQ of 58.

### **Main results obtained:**

Array-CGH detected a 12 kb deletion on chromosome 22q13.3 involving SHANK3 in the mother, the twin brothers and the daughter.

### **Conclusions:**

To date, this is the first report of an affected individual with SHANK3 interstitial deletion able to reproduce. Moreover, we speculate about the association between SHANK3 deletion and UBOS-like brain lesions.

**A TRIAD OF INFANTILE SPASM, BINOCULAR NYSTAGMUS AND FOCAL TONIC SEIZURE**

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**Introduction:**

Epileptic spasms represent a subcategory of motor seizures that has been extensively documented and atypical characteristics are continuously being identified through case reports, questioning its classification and underlying pathophysiology. The temporal and spatial relationship between focal seizures and epileptic spasms represents one such questioning.

**Case report:**

We report the findings in an infant with a triad of clinical manifestations during one single ictal event, comprising a cluster of epileptic spasms, intermixed with binocular vertical nystagmus and a focal tonic seizure. Our observations are illustrated with a video-recording that enables clinical data to be correlated with EEG modifications. Brain imagery did not identify a focal lesion, and genetic analyses are pending. The child has responded very well to low doses of vigabatrin. Development has remained within normal limits up to now.

**Discussion:**

The co-occurrence of these ictal paroxysms during the same event has not been reported previously, to our knowledge. This observation extends the range of clinical manifestations associated with epileptic spasms, and underlines the gap of knowledge that needs to be filled in our understanding of underlying pathophysiological mechanisms of that type of seizures.

**DYSTONIE DE TYPE 11 A DEBUT PRECOCE**

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VIDÉO

La dystonie de type 11 (Myoclonus-Dystonia) est un trouble du mouvement caractérisé par l'association de contractions musculaires brèves, rapides (myoclonies) et de mouvements répétitifs et soutenus de torsion ce qui induit une posture anormale (dystonie). La maladie débute habituellement avant 20 ans. La transmission est autosomique dominante avec mutation du gène de l'Epsilon-Sarcoglycan. Habituellement, le gène hérité de la mère n'est pas exprimé alors que celui hérité du père l'est. La transmission du gène est donc soumise à un mécanisme d'empreinte maternelle. La prévalence est estimée à 1/500000 en Europe.

Nous rapportons le cas d'un garçon qui consulte à l'âge de 6 ans en raison d'un phénomène de torsion et de crispation se manifestant dans l'exécution de certaines tâches motrices, avec répercussion sur le graphisme et les gestes requérant une dextérité fine. Cet enfant n'a pas d'antécédent familiaux ni personnels particuliers et il a franchi les étapes du développement psychomoteur normalement avec notamment l'acquisition de la marche à 14 mois. A l'époque, l'examen montrait une certaine raideur dans les mouvements, un électroencéphalogramme et une IRM cérébrale normaux et seule de la rééducation psychomotrice a été instaurée. L'enfant n'a reconsulté qu'à l'âge de 8 ans ½ : en raison de ses troubles moteurs induisant une dysgraphie, ainsi qu'en raison d'un T-DAH, l'enfant avait été orienté vers un enseignement spécialisé pour les enfants présentant des troubles instrumentaux. L'examen clinique actuel montre : d'abondantes secousses myocloniques et de discrets mouvements choréiques prédominant aux membres supérieurs, et des mouvements anormaux s'apparentant à une dystonie tâche dépendante lors de certaines actions, surtout l'écriture (cf vidéo). La recherche génétique de dystonie de type 11 est revenue positive : hétérozygote pour la mutation pathogène c.344A>G, p. (Tyr115Cys) dans l'exon 3 du gène SGCE. La sœur âgée de 6 ans présente la même mutation mais le phénotype est dominé par des manifestations myocloniques. Les parents n'ont pas souhaité être testés.

Plusieurs traitements ont été essayés sans succès : L-dopa, Clonazépam, Primidone. Un essai est en cours avec du Zonégran avec une efficacité qui semble un peu meilleure. Le valproate, le lévétiracétam, le topiramate, les traitements anticholinergiques, le L-5-hydroxytryptophane, la toxine botulique pourraient être envisagés. L'ingestion d'alcool est efficace mais bien sûr non recommandée. La stimulation cérébrale profonde du globe pallidal interne et/ou du noyau intermédiaire ventral du thalamus a montré son efficacité dans certains cas, avec semble-t'il une efficacité meilleure pour la stimulation du globe pallidal interne.

Conclusion : la dystonie de type 11 est un trouble du mouvement rare, à début précoce et invalidant. Le diagnostic permet une prise en charge adaptée et améliore la qualité de vie des personnes atteintes.

## ACUTE UNILATERAL OPHTHALMOPARESIS ASSOCIATED WITH ANTI-GQ1B AND GM1 ANTIBODIES AFTER PARVOVIRUS INFECTION IN A 10-YEAR-OLD GIRL

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**Introduction:** we present a paediatric case of acute unilateral third cranial nerve palsy in the absence of any other neurological clinical sign or any neuro-radiological findings. Raised titers of immunoglobulin M antibodies against GM1 and GQ1b ganglioside components were demonstrated as well as specific immunoglobulin M antibodies against parvovirus B19.

**Case Report:** A 10-years-old girl was admitted at the Emergency Department of our Paediatric Hospital, because of acute-onset of unilateral ophthalmoparesis, diplopia and ptosis. Her personal history was unremarkable. On admission clinical evaluation revealed left ptosis, left inferior oblique muscle deficit (uncomplete extrinsic paresis of left third cranial nerve) and anisocoria with left myidriasis with no reaction to light and accommodation (complete intrinsic paresis of left third cranial nerve). The other cranial nerves were normal, no other neurological signs were detected.

She had experienced a flu-like syndrome ten days before, without fever.

Findings from computed tomography (CT) and magnetic resonance imaging (MRI) of brain and orbit with angio-MRI study were normal. Routine laboratory tests were normal as well.

Cerebrospinal fluid antibodies against Citomegalovirus, Epstein-Barr virus, Herpes simplex virus type 1 and 2, Enterovirus, Adenovirus, Parvovirus, Herpes virus 6, Varicella virus, JC virus and Borrelia were negative. The only laboratory abnormality was the plasma PCR for Parvovirus B19 with antibodies isotype M (800 viral genomes/mL) and serum IgM titer to GM1 (borderline value) and to GQ1b (1/800 with normal value <1/400).

The girl was given oral prednisone (2mg/kg daily) for ten days, then tapering with complete resolution of left oculomotor nerve palsy in one month and a half.

Two months after the onset IgM serum titer to GM1 and to GQ1b were normalized.

### Conclusions:

With this case-report we would underline the peculiar correlation between neurological isolated sign and recent parvovirus B19 infection.

Parvovirus B19 neurological manifestations and its role in the pathogenesis of autoimmunity are well known. Acute cranial nerve mononeuritis is rarely associated with parvovirus B19, which has not been linked to third cranial nerve involvement. On the other hand, anti GQ1b antibody positivity apart from classic Miller-Fisher syndrome is associated with ophthalmoplegia without ataxia and also with cranial nerve unilateral mononeuritis. No association between parvovirus B19 and anti GQ1b antibody positivity has been described in the literature.

The dysimmune pathogenesis of the ophthalmoparesis in our patient is clearly demonstrated by the cross-reacting antiganglioside antibodies. Moreover, the patient rapidly improved on oral prednisone.

# O15

## GRADUAL BRAIN INVOLVEMENT IN FETAL TSC

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### Objective:

CNS Tuberosclerosis (TSC) a systemic, autosomal dominant genetic disorder is characterized by brain lesions where balloon cells can be considered as histopathological hallmarks.. We purpose here the development shedule of TS lésions constitution.

### Methods:

We analysed 12 fetal and perinatal brains (from 21 GW until 3days after birth) with TSC lesions. For each patient we considered: 1) the type of cell lesion 2) their nature (using both glial and neuronal markers) 3) their cytoarchitectural and 3) spatial organization.

### Results:

We identified 3 types of TSC Cells (b cells, balloon cells (BC) and dysplastic giant neurons (DN) and 3 types of cytoarchitectonics (A and B cocards, , cortical tubers). Cells were characterized using neuronal and glial markers. While b cells were exclusively neuronal, balloon cells could be both , the glial ones being proeminent and appearing earlier during pregnancy. DN and cortical tubers are respectively observed are observed after 25GW and 30GW. Type A cocard remained located on periventricular area while type B cocarde evolved with age and progressively occupied more superficial white matter areas. Both contained glial and neuronal BC. Cortical BC are firstly observed at 25GW on layer I, and were present in all layers after 30GW.

### Conclusion:

Our study demonstrate that in fetal brain TSC lesions evolved progressively following distinct patterns according to their location or the TSC cell nature.



# DCC1

## A RARE CAUSE OF INTRACRANIAL HYPERTENSION

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**Objectives:** to describe an unusual cause of intracranial hypertension in a child aged 9 months, addressed to MRI for symptoms of intracranial hypertension (vomiting, fontanel bulging), hypotonia, and sleep disorder. A ventriculoperitoneal shunting was placed following several episodes of intracranial hypertension, despite serial lumbar punctures.

**Main results:** MRI shows a diffuse meningeal enhancement, associated to parenchymal abnormalities, which address the possible diagnosis, confirmed by cortical and meningeal biopsy.

# DCC2

## THE CONTRIBUTION OF NUMERICAL COGNITION ASSESSMENT IN DIFFERENTIAL DIAGNOSIS BETWEEN VISUO-SPATIAL VERSUS EXECUTIVE DISORDER IN CHILD WITH DEVELOPMENTAL COORDINATION DISORDER

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In children with Developmental Coordination Disorder, it is often difficult to determine if this disorder depended on the visuo-spatial or the executive component. When the children present difficulties in arithmetic, the evaluation of their construction and their use of the number by numerical cognition assessment, should help to the differential diagnosis, so allowing to identify if these difficulties recovered from visuo-spatial and/or executive disorder.

We presented a case of a 9-year old male child with learning disabilities and mainly calculation disorders for which he had never benefited from reeducation in this domain. The results of the multidisciplinary assessment of our team allowed to diagnose first of all a visuo-spatial dyspraxia associated with Attention Deficit Hyperactivity Disorder (ADHD). The numerical cognition assessment, realized secondarily, was in favour of an essentially executive of the digital cognition. We then made the hypothesis that the first evaluation had been disrupted by the impulsiveness, and the disorder of attention and planning of this child. So, the first diagnosis of visuo-spatial dyspraxia associated with ADHD was ruled out and visuo-spatial dyspraxia was considered as a consequence of ADHD.

In conclusion, we can say that the neuropsychological assessment of numerical cognition in child with Developmental Coordination Disorder could help to the differential diagnosis between visuo-spatial and executive disorder, essential step before any therapeutic adjustment.

## SEIZURES SYMPTOMATIC OF A CALCIFIED LESION. DIAGNOSTIC AND THERAPEUTIC APPROACH

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### Study objectives:

To report about a case of seizure symptomatic of a brain calcified lesion with perilesional edema. To discuss: 1) the differential diagnosis and the significance of brain tissue calcification; 2) the neuroimaging criteria needed for a definite diagnosis; 3) the pharmacological/surgical treatment.

### Methods:

A 15 years girl presented a first focal epileptic seizure, followed by a second seizure that occurred after 2 hours while an urgent EEG was been performed. The ictal semeiology was represented by a vague inaugural lightness sensation, followed by painful sensation then by an increased muscle tone at the right leg. The seizure rapidly evolved to a bilateral convulsion. The EEG was coherent with clinical signs showing focal ictal activity starting from the left centro-parietal areas. The intercritical neurological examination was normal but the girl continued to refer the impression that her right leg was "different" from the left one.

### Main results obtained:

The MRI showed a small single lesion localized near the subarachnoid space along the interemispheric scissure in the left parietal lobe. The lesion displayed enhancement in a ring pattern after contrast medium administration and was surrounded by a significant edema even if not displacing midline structures. The CT confirmed a small, rounded, well-defined calcification. Diagnostic schedule was completed with X-ray chest, ultrasound abdomen, eye examination, Toxoplasma, HIV, Taenia solium serology, Mantoux, MRI spectroscopy, spinal cord MRI.

### Conclusions:

The girl was treated with antiepileptic drug (carbamazepine) and steroids. She had no more seizures and the subjective symptoms disappeared. Brain edema resolved. The topics that need a further discussion are: 1) the role of brain calcification, the role of edema and inflammation in leading to seizures; 2) the role of treatment (antiepileptic, anti-inflammatory) in preventing seizures recurrence (epileptogenesis) in a specific contest.

# DCC4

## A COMPLICATED AND PUZZLING COURSE OF A CRYPTOGENIC EPILEPSY: A NEURODEVELOPMENTAL DISORDER OR A NEURODEGENERATIVE DISEASE ?

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### Le but :

Discussion du diagnostic différentiel d'une forme d'épilepsie à cause inconnue se manifestant dans l'enfance, accompagnée d'un trouble du mouvement progressif, de symptômes neuropsychiatriques et de déficits neuropsychologiques évoluant vers un retard mental.

### La méthodologie :

Un jeune garçon de 11 ans, avec un retard du langage, a sa première crise épileptique à l'âge de 8 ans. A ce moment-là, il a un niveau intellectuel normal, l'examen neurologique ne montre pas de signes focaux : l'enfant est juste légèrement maladroit dans l'exécution motrice. L'évolution du cadre clinique s'aggrave lentement, manifestant au fil des années des difficultés d'apprentissage et un trouble de la coordination motrice avec dysgraphie sévère. Sur le plan émotionnel et comportemental, le développement de l'enfant est compliqué par l'émergence d'un trouble de la socialisation (anxiété sociale, isolement, bizarreries dans le langage et dans le comportement).

### Les principaux résultats obtenus :

Les examens de premier niveau effectués au début d'épilepsie sont normaux. Les données electro-cliniques ne sont pas spécifiques ni décisives pour une classification syndromique et initialement on suppose une forme d'épilepsie d'origine génétique ou du développement. Pendant les deux années suivantes, les crises épileptiques sont contrôlées grâce au traitement anti-épileptique. Toutefois, un dysfonctionnement cognitive et social se manifeste progressivement. Sur le plan moteur, la maladresse s'aggrave ; l'évaluation de la motricité fine révèle un trouble du mouvement avec dyskinesies. L'EEG est encore caractérisé par un ralentissement de l'activité de fond avec des paroxysmes de pointe-onde diffuses, comme au début de l'épilepsie. L'IRM cérébrale est normale.

### Conclusions :

L'épilepsie a été traitée avec des médicaments anti-épileptiques (lamotrigine et clobazam) qui ont été suffisamment efficaces. Actuellement, les problèmes provoquant l'invalidité majeure sont liés au trouble du mouvement, aux difficultés scolaires et au dysfonctionnement social. Le trouble du mouvement touche principalement la motricité fine et il répond que partialement au traitement avec bêtabloquante. La discussion porte sur : 1) la qualité du mouvement (coordination motrice, mouvements anormaux) et sa classification diagnostique ; 2) le rôle des symptômes neuropsychiatriques et du trouble du mouvement dans le diagnostic différentiel de cette forme d'épilepsie ; 3) l'hypothèse d'une maladie neurodégénérative parmi les causes d'une forme d'épilepsie avec trouble du mouvement.

# DCC5

## UN COMA NÉONATAL PROGRESSIF

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1<sup>er</sup> enfant né au terme de 37SA après rupture précoce des membranes.

Ictère néonatal à J2 mise sous photothérapie

J4 : enfant geignard, hypotonique, tachycarde ; perte du contact et de la tétée ; perte de 12% du poids /naissance

Appel du SAMU : enfant en opistotonos, myosis serré, pas ce contact, mouvements d'enroulement.

## CENTRAL NERVOUS SYSTEM (CNS) DEMYELINATING DISEASES IN CHILDHOOD: A REPORT OF 14 CASES

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### Objective:

Aim of the study is to describe clinical, laboratory and neuroimaging features, treatment and outcome of consecutive patients with paediatric CNS acquired demyelinating syndromes (ADS) in our Institute between 2012 and 2016.

Introduction: ADS can be difficult to diagnose in children and adolescents because of the heterogenous clinical presentation. There is a lack of cohort studies.

### Material and methods:

The sample consisted of 14 cases (7 males and 7 females, mean age at onset 9.1 years, range 23 months- 13 years). The assessments included neurological examination, blood and cerebral spinal fluid (CSF) analyses and neuroimaging (cranial and spinal magnetic resonance imaging MRI).

### Results:

Most patients had more than one symptom: inferior or superior limb pain/paresthesia (35,7%), gait impairment and vomit (28,5%), drowsiness (21,4%), headache aphasia and dysarthria (14%). Neurological evaluation revealed: weakness (28%), hyporeflexia (28%), altered sensitivity (14%), nystagmus (7%), hyperreflexia (14%), balance disorder (14%), hypotonia (21%), hemiparesis (14%), clumsiness (14%), cranial nerves deficit (14%), strabismus (7%) and urinary retention (7%). CSF examination was performed in 86% of cases, with negative Link index in 84% of them and presence of oligoclonal bands in 38% of them. Antibodies antiacquaporine 4 were performed in 15%, positive in 7% while Anti MOG antibodies were performed in 15%, all negative. EEG was performed in 66% of cases with pathological result in 70% of them.

All patients had brain MRI, with variable findings. The most affected cerebral areas were: frontal and frontoparietal subcortical white matter, temporal gyrus, bulb, corona radiata, thalamus and medulla. After 1-3 months of treatment, MRI findings improved in 60% of cases, but in 13% of cases new lesions were detected. In 8 cases, the MRI was repeated after 6 months revealing improved findings in 60% of them. Clinical evaluation and MRI findings permitted us to make diagnosis of Acute Disseminated Encephalomyelitis (ADEM) in 50%, Multiple Sclerosis (MS) in 14%, Clinically Isolated Syndrome (CIS) in 14% and Transverse Myelitis (TM) in 22%. Steroids therapy was associated with a rapid recovery and both intravenous high dose methylprednisolone and dexamethasone were similarly effective. One patient also received intravenous IG and plasma exchange. All patients have survived. Eight patients recovered completely, five children had mild sequelae and one child is still in acute phase.

### Conclusions:

The data from these consecutive paediatric ADS cases underscore the diversity of the clinical presentation and MRI findings, and document a protracted course of illness with a generally positive prognosis.



**FLUCTUATING PTOSIS AND GENERALIZED WEAKNESS ASSOCIATED WITH PSEUDO-INTERNUCLEAR OPHTHALMOPLEGIA AND VERTICAL MISALIGNMENT IN A CHILD: A CASE OF JUVENILE MYASTHENIA GRAVIS**

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**Study objectives:**

To present a case of pre-pubertal Juvenile Myasthenia Gravis (JMG) with atypical ocular presentation. JMG is a rare antibody mediated autoimmune disorder of the neuromuscular junction, resulting in skeletal muscle weakness and fatigability. The disease can affect only extraocular muscles or it can be generalized. Treatment is controversial: Acetylcholinesterase (AChE) inhibitors are the first-line treatment, immunosuppressive and immunomodulating drugs can be used, thymectomy can be a choice in acetylcholine receptor antibodies (AChR-Ab) positive generalized JMG.

**Methods and results:**

We report the case of a 4-year-old boy with fluctuating ptosis, generalized weakness and diplopia. At neurological and ophthalmological evaluation pseudo-internuclear ophthalmoplegia and vertical misalignment were documented. Family medical history was significant for autoimmune diseases. Full blood count, serum chemistries, serum lactate, thyroid function tests, catecholamine urine test, neuron-specific enolase, cranial Magnetic Resonance Imaging (MRI) and magnetic resonance angiography were normal. Serum AChR-Ab titres were elevated. A 3 Hz repetitive nerve stimulation test examination and an electromyographic examination revealed normal results (poor child compliance). Thoracic computed tomography documented normal thymic gland but a possible ectopic thymus. Clinical diagnosis of generalized JMG was confirmed. Therapy with pyridostigmine was started with clinical benefits but only partial. After 3 months from diagnosis the child underwent thoracoscopic thymectomy (normal at histological examination). After 6 months from thymectomy there is a better control of symptoms but continuation of drug therapy is required and Ab titres are still elevated.

**Conclusions:**

JMG can mimic severe diseases with higher incidence (neoplasm, inflammatory, or vascular diseases). At our knowledge there is no previous description of JMG manifesting also with vertical misalignment of eyes, and few adult patients are reported. Although rare, myasthenia should be considered in children who present with variable weakness, ptosis or ophthalmoplegia. Diagnosis remains clinical and diagnostic tests could be negatives. An early diagnosis is important because patients can be successfully treated. Management must take into consideration patient's degree of disability, chance of remission, and treatment-related risk. In AChR-Ab positive generalized JMG thymectomy must be considered. Multicenter studies comparing the responses of treatment in pre-pubertal and post-pubertal patients and long-term immunological follow-up would help to establish more specific indications for thymectomy.

**PSYCHOMOTOR SLOWING AS THE EMERGING SYMPTOM OF MILD ENCEPHALOPATHY WITH REVERSIBLE SPLENIAL LESION (MERS): A CASE REPORT**

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A 12-year-old boy was admitted to OIRM's Intensive Unit Care because of two convulsive episodes followed by psychomotor agitation and altered consciousness. Neurological symptoms became prominent on day six after a flu episode with vomiting, high fever and a lipotimic attack. Previous medical history was unremarkable. During the hospitalization, his neurological findings were normal, except for a psychomotor slowing with absence of speech. CSF analysis revealed mild pleocytosis and high level of protein. A CT study of the brain was normal, despite of a global slow activity on electroencephalography.

An EBV genome replication and an elevation of M antibody subtype against EBV and HSV6 were detected in serum, but not in CSF.

Intravenous ceftriaxone, fluconazole, and acyclovir were started on the day of admission due to persistent disturbance of the level of consciousness and suspected acute encephalitis. Furthermore, dexamethasone 0.4 mg/kg/day and antiepileptic prophylaxis were started. Brain MRI performed on day 2 of neurological symptoms onset showed a focal hyperintensity in the splenium of the corpus callosum on T2 images with corresponding diffusion restriction on Apparent Diffusion Coefficient (ADC) mapping, suggestive of an intramyelinic oedema. His clinical condition, in particular cognitive-motor slowing, improved over the subsequent ten days, with an improvement of MRI lesion and of electroencephalographic activity. Clinical recovery was complete, no neurological signs were evident on discharge and on the following 4 months of follow-up.

The MRI findings, in association with the favourable prognosis of an acute encephalopathy, point to a specific clinico-radiological syndrome, "Mild Encephalopathy with Reversible Splenial Lesion" (MERS), whose recognition is important also in order to avoid unnecessary treatment.





## INTRAOPERATIVE SEIZURES OCCURRENCE DURING BRAIN MAPPING TECHNIQUES FOR ELOQUENT AREA TUMORS SURGERY: DATA FROM A PEDIATRIC NEUROSURGICAL CENTRE

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### Study objectives:

To report on the incidence of intraoperative seizures during brain mapping techniques for eloquent area tumors surgery in a pediatric neurosurgical center. Intraoperative mapping techniques are fundamental for achieving both large surgical resection of brain tumors in eloquent areas, to improve oncological prognosis, and functional preservation, to maintain an optimal postoperative functional status. Intraoperative seizures are a matter of concern since they can interfere with functional mapping, provoke status epilepticus and be cause for premature interruption of tumor resection. A discrepancy is documented between guidelines, which do not support the use of perioperative pharmacological seizure prophylaxis, and clinical practice in many centers, which use it (mainly with levetiracetam). Moreover, there is large variability among centers concerning the type of mapping techniques and seizure management. All published data about occurrence of intraoperative seizures, risk factors and pharmacological management refer to adult patients. In a recently published European multicenter survey, the incidence of intraoperative seizures varied significantly, ranging from 2.5% to 54%. History of preoperative seizures and mastery of mapping techniques were related with the risk of intraoperative seizures, without documented association with use of perioperative pharmacological prophylaxis.

### Methods:

The data from all the pediatric patients undergoing supratentorial brain tumor resection with intraoperative mapping techniques from 2010 to 2016 at the Regina Margherita Children Hospital of Turin were analyzed. All patients underwent an asleep surgery procedure with transcutaneous EEG (tcEEG) and electrocorticography (ECoG) recording. Cortical mapping was performed using subdural strip or monopolar stimulator.

### Results:

Of 99 surgical tumor resections with intraoperative monitoring and mapping techniques, 25 regarded supratentorial tumors in eloquent areas (mean age 9 years and 6 months, ranging from 1 years and 2 months to 18 years). No pharmacological prophylaxis was used unless preoperative seizures were documented (12 patients of 25). Three patients had intraoperative seizures, 2 of them on pharmacological treatment for preoperative seizures.

### Conclusions:

The estimated incidence of intraoperative seizures in pediatric patients with supratentorial tumors is about 12% (95% C.I. 4-30%). A conservative estimate suggests that up to 1 in 3 may suffer a intraoperative seizure, underscoring the need for further identifying specific risks and developing effective prevention. In pediatric neurosurgical centers pharmacological prophylaxis is not routinely used. Multicenter data collection focused on children would help to establish the real occurrence of intraoperative seizure, risk factors and utility of pharmacological prophylaxis.

**GLUT1 DS: THE COGNITIVE ASPECTS**

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**Aim of study:**

Glucose transporter type 1 deficiency syndrome (GLUT1DS) is a genetically determined, treatable, neurologic disorder caused by insufficient transport of glucose into the brain, due to mutation in SCL2A1 gene. Ketogenic diet (KD) is the gold standard treatment for GLUT1DS. Classical symptoms are represented by epilepsy, movement disorder and cognitive impairment described as a mild to moderate-severe mental disability. The aim of this study is cognitive characterization of patients with GLUT1DS.

**Methods:**

We present a retrospective study involving 25 patients (7 males and 18 females) with established diagnosis of GLUT1DS, aged 3.7-40 years (mean 13.25), treated with KD and followed at IRCCS Mondino of Pavia between 2007 and 2016. Standard cognitive tests with Wechsler Intelligence Scales were conducted at T0 (before introduction of KD), T1 (18 months since KD introduction) and T2 (49 months since KD introduction). Clinical characteristics analyzed in relation to cognition were the type of mutation, cerebrospinal/blood glucose ratio, and patient's age at the time of KD introduction.

**Results:**

IQ scores at T0 were available in all patients. Mean scores were: total IQ (TIQ) 66.8 (range 40-99), verbal IQ (VIQ) 75.32 (range 45-118), performance IQ (PIQ) 68.96 (range 45-98). Cognitive data at T1 were available for 14 patients, which demonstrated an improvement in TIQ from 61.1 to 63.14, in VIQ from 68.1 to 73.42 and a stationary PIQ (from 64.7 to 64.64). Moreover we observed that a positive evolution of the cognitive outcome is directly proportional to an early age of KD introduction and to a higher CSF/blood ratio value.

Cognitive data at T2 were available for 6 patients. All patients demonstrated an improvement in all IQ domains (TIQ, VIQ, and PIQ), even in those with a very low CSF/blood ratio value.

**Conclusions:**

Our data clearly demonstrate a characteristic cognitive profile of GLUT1DS patients who presented an intellectual disability (demonstrated in 85,1%) with PIQ more affected than VIQ. KD showed to improve visuo-motor precision, alertness, sensorimotor speed, performances. The best response to KD in short term is in patients with higher CSF/blood ratio, which remains constant in medium term. Otherwise, for patients with "lower ratio" there is a medium term positive response, although not as significant as in higher ratio group. Early KD introduction resulted in greater cognitive improvement. Our data confirmed indication to continue KD for long time in order to increase chances of intellectual disability improvement.



## PAEDIATRIC GLIOMATOSIS CEREBRI: CLINICAL PRESENTATION, PROGNOSTIC FACTORS AND APPROPRIATE MANAGEMENT

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### Study objectives:

Gliomatosis cerebri is a rare, diffusely infiltrating glial neoplasm with a highly variable presentation, poorly defined clinical course, and typically fatal outcome. Its rarity makes it difficult to define prognostic factors and appropriate management. In literature the vast majority of the patients reported are adults. We report our experience at Gaslini Institute of 15 patients with gliomatosis in order to better define clinical presentation, prognostic factors and appropriate management.

### Methods:

We retrospectively reviewed the databases of Gaslini Institute between 1995 and 2013 and we select 15 patients with primary gliomatosis. We collected data about EEG, MRI and Lansky Performance Status. Progression free survival and overall survival were calculated according to Kaplan-Meier method.

### Main results obtained:

We found a slight male predominance in children. This seems to support the fact that males present earlier onset. In addition, prognosis seems to be gender correlated. The majority of patients were diagnosed between the 1st decade of life.

Early onset doesn't seem to affect prognosis.

Lansky Performance Scale at diagnosis and presence of low grade glioma correlated strongly with overall survival. In our series, gliomatosis is mainly bilateral and it seemed to have predilection for the right side of the brain.

Central nervous system involvement mainly concerned hemisphere, followed by thalamus, basal ganglia and brainstem. Presence of enhancement on MRI did not seem to predict prognosis. Clinical presentation at onset is really variable. Seizures are the most frequent symptoms. We focused attention on psychiatric disorders: in fact they constitute 20% of clinical presentation, but often they are not properly investigated. For this reason, diagnosis and, consequently treatment can be delayed.

EEG patterns is often characterized by generally disorganized background activity and, sometimes, by focal or multifocal epileptic abnormalities.

Among antiepileptics drugs, levetiracetam seems to be the best choice even because there are not interactions with chemotherapy.

Overall survival between patients treated with chemotherapy alone and patients treated with both chemotherapy and radiotherapy is not significantly different.

### Conclusion:

In conclusion, gliomatosis is an extremely variable disease because of type of onset and clinical symptoms and therefore it should be difficult to recognize. Clinical presentation, prognostic factors and appropriate management are discussed.

## AICARDI-GOUTIÈRES AND SINGLETON-MERTEN SYNDROMES: AN OVERLAPPING PHENOTYPE ASSOCIATED WITH A GAIN-OF-FUNCTION MUTATION IN IFIH1

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IFIH1 (also known as MDA5) is a key component of the antiviral type I interferon-mediated innate immune response, coding for a cytosolic receptor of double-stranded RNA.

Heterozygous gain-of-function IFIH1 mutations have been recently described to cause a spectrum of neuroinflammatory phenotypes including Aicardi-Goutières syndrome (AGS) and non-syndromic spastic paraparesis, but also apparently non-neurological phenotypes – most particularly Singleton-Merten Syndrome (SMS). SMS is a multisystem disease characterized by calcification of the aorta and cardiac valves, dental abnormalities (periodontitis, delayed dental eruption and early loss of permanent teeth) and bone disease (osteopenia, acro-osteolysis). So far, less than 25 cases have been described in the literature, some of which have been proven to be due to heterozygous missense mutations in IFIH1. As for IFIH1-related neuroimmunological phenotypes already described, mutation-positive patients with SMS demonstrate a marked induction of type I interferon signaling.

Here we report a young male who expressed a phenotype involving the skin, dentition and nervous system (both peripheral and central). The presence of delayed myelination associated with cerebral calcification on cranial imaging led to the suspicion of AGS, the execution of an “interferon signature” and the detection of a de novo heterozygous mutation in IFIH1 (c.992C\_G/p.Thr331Arg).

Even considering the presence of neurological involvement characterized by cognitive impairment, spastic-dystonic quadriplegia and dysarthria, several clinical findings in this patient were considered atypical for a diagnosis of AGS. Specifically, growth retardation in the absence of microcephaly, a sensory-motor polyneuropathy, the presence of psoriatic-like skin-lesions, a cleft lip and palate with delayed dental eruption and early loss of teeth.

These latter features being more suggestive of SMS.

Our case further extends the phenotypic spectrum associated with mutations in IFIH1, which comprise features of both AGS and SMS – likely reflecting a common pathogenic IFIH1-related pathway.



**CYCLIC VOMITING IN PATIENT WITH NEUROFIBROMATOSIS**

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**Background** Cyclic vomiting Syndrome is characterized by acute, intense, episodic vomiting interspersed with periods of normal health; attacks usually last from hours to days, have a certain periodicity and are stereotyped within an individual. This disorders is idiopathic and included in "childhood periodic syndrome" or "migraine variant", according the International Classification of Headache Disorders III edition. It should be differentiate from other causes of symptomatic vomiting which can mimic its presentation, such as metabolic disease.

Neurofibromatosis type I is the most common Neurocutaneous Syndrome. Cafe´ au lait macules, skin fold freckling, osseous lesions, Iris hamartomas (Lisch nodules) and predisposition for the development of benign and malignant tumors involving neural and non-neural tissues are the main features. Central nervous system neoplasms represent a significant portion of these malignancies and manifest primarily in children less than 10 years of age.

**Study objectives:**

We describe the clinical case of a 9-year-old child with Neurofibromatosis type I (NF1) and episodes of cyclic vomiting with headache since the age of 4. The boy underwent gastroenterological evaluation and imaging (MRI) studies.

**Results:**

The child had recurrent stereotype episodes characterized by intense headache and repetitive vomiting, lasting about 10-12 hours.

The paroxysmal episodes used to manifest approximately every 10 days and the patient was asymptomatic between them. On neurological examination he presented pyramidal signs (brisk reflexes, left Babinski sign) and strabismus. MRI had already been performed elsewhere showed multiple focal abnormal signal intensity (FASI), which are a characteristic finding in NF1, usually found during childhood and typically decreasing with age. According to the clinical presentation, a Cyclic Vomiting Syndrome was diagnosed.

During the hospitalization in our department, he underwent a new MRI, which showed an increase of one lesion in the right dorsal portion of the bulb (TR sequences), that appeared slightly swollen. Because of these radiological features, a low-grade glioma was hypothesized.

**Conclusion:**

We will discuss the possible etiological causes of the child's symptoms and the therapeutic options. We underline that neuroimaging in NF1 should be guided by clinical assessments and it's mandatory whenever this disease manifests with an atypical presentation.

## POST-VARICELLA ANGIOPATHY: A FREQUENT BUT UNDERESTIMATED CAUSE OF INFANTILE STROKE WITH GOOD PROGNOSIS

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### Introduction:

Arteriopathies are the most common cause of stroke in children. Among them, focal cerebral arteriopathy may represent the end result of a variety of underlying pathophysiological mechanisms yielding the same radiologic appearance.

### Case report:

A previously healthy 4-year-old girl was admitted to our hospital for headache and speech disorder. Her medical history was irrelevant except for Varicella Zoster Virus (VZV) infection seven months before. Three days before admission, short lasting headache attacks appeared acutely. On the day of admission, the patient had severe headache and speech difficulties. Physical and neurological examination on admission were significant for non-fluent aphasia and word-finding difficulties, which spontaneously recovered in about six hours. Routine blood tests, echocardiogram and electrocardiography were normal.

Brain imaging showed focal cerebral arteriopathy with stenosis of the proximal segment of the left middle cerebral artery and a hypodense area consistent with ischemic stroke in the left parietal cortex and insula.

Further thrombophilia screening revealed LAC positivity, increased factor VIII levels and G20210A prothrombin heterozygotic mutation. Autoimmune and metabolic markers, haemoglobin electrophoresis, serology for Echovirus, Coxsackie, HIV, EBV, B. burgdoferi were all negative. A positivity for VZV-IgG was detected. Cerebrospinal fluid - proteins, cell count, glucose, PCR for principal neurotropic viruses including VZV, Link's index, Reiber formula, oligoclonal bands - was normal, but intrathecal virus-specific antibodies analysis documented intrathecal synthesis of IgG against VZV. A diagnosis of post-Varicella angiopathy was made, according to the proposed diagnostic criteria (Sébire 2004): radiological findings of unilateral focal cerebral arteriopathy (involving the distal part of the internal carotid artery and the initial segments and branches of the anterior and middle cerebral arteries), absence of a long-term progression, history of Chickenpox within the previous 12 months.

Definitive diagnosis was made by detection of anti-VZV IgG antibody in the cerebrospinal fluid. Therapy with acetylsalicylic acid (5mg/kg/die) was started.

One month later, MRI showed regression of parenchymal abnormalities, as well as decrease of the stenosis. At 18-months follow-up, the patient was still under therapy; there was no evidence of new clinical events, or new MRI alterations.

### Conclusion:

VZV usually causes a self-limiting disease. However, it can determine many complications also in immunocompetent children.

Although rare, central nervous system complications should be suspected in children with a history of chickenpox and acute neurological signs. In a case of arterial ischemic stroke, post-Varicella arteriopathy has to be considered. Diagnostic workup should include cerebrospinal fluid examination for VZV-DNA and VZV specific antibodies.



**DRAMATIC RELAPSE OF SEIZURES AFTER EVEROLIMUS WITHDRAWAL**

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Tuberous sclerosis complex (TSC) is an autosomal dominant multisystemic disorder caused by deregulation of the mTOR pathway, and represents one of the leading genetic causes of epilepsy.

mTOR inhibitors (Sirolimus and Everolimus) are currently approved only for the treatment of growing subependymal giant cell astrocytomas (SEGA), renal angiomyolipomas and lymphangiioleiomyomatosis in TSC. However, preclinical and clinical evidence supports their potential role in effectively treating TSC-associated epilepsy, but no consensus on its use in seizures has been reached yet, and there are few data on epilepsy outcome after the suspension of mTOR inhibitors treatment.

We present the case of a 15-year-old girl with TSC whose diagnosis was established in childhood after the onset of focal seizures, which were rapidly controlled by Vigabatrin. Brain MRI showed multiple cortical and subcortical tubers, white matter radial migration lines, subependymal nodules, and a SEGA located near the right foramen of Monro, which was slowly growing, as seen on serial MRIs. Treatment with Everolimus was started at age 12 years, leading to 30% volume reduction of the SEGA after 6 months of treatment. Everolimus was withdrawn 27 months later, and the patient experienced an abrupt relapse of seizures. Treatment with the mTOR inhibitor was then restarted, with control of seizures without changing antiepileptic drugs (AEDs). One year later, Everolimus was temporary withdrawn for a severe gastroenteritis with increase of liver enzymes. The first day after suspension, the patient experienced again immediate seizure relapse. Everolimus was restarted after the resolution of the gastroenteritis, but seizures persist monthly, even after increasing the AEDs.

We report for the first time on a patient in whom discontinuation of Everolimus (prescribed for a growing SEGA) was associated with a dramatic relapse of seizures twice. This clinical report supports the promising potential of Everolimus in treating epilepsy in TSC, and specifically underlines.

## NOUVELLE MUTATION DU GÈNE CCDC22 RESPONSABLE D'UN SYNDROME DE DANDY WALKER SYNDROMIQUE, LIÉ À L'X

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Le syndrome de Dandy Walker (DW) est une malformation cérébelleuse définie sur des critères morphologiques, radiologiques ou neuropathologiques. Il est caractérisé par une hypoplasie et une rotation vers le haut du vermis cérébelleux, une dilatation kystique du 4ème ventricule et une fosse postérieure élargie avec une surélévation de la tente du cervelet.

Cette définition explique la grande variabilité de sa symptomatologie clinique, et ses étiologies diverses (infections congénitales, anomalies chromosomiques et récemment monogéniques).

Nous rapportons 2 frères présentant les critères radiologiques de DW, issus d'un couple non apparenté.

Chez le plus jeune, le diagnostic a été posé en prénatal et une hydrocéphalie a nécessité dès 6 semaines 2 interventions chirurgicales. Ils ont présenté une hypotonie, un retard des acquisitions et une dysmorphie faciale et des extrémités. Actuellement, âgés de 19 ans et 8 ans, leur QI est entre 40 et 45 ; l'ainé en IME est autonome pour sa toilettes et ses déplacements en transport en commun, il a une scoliose, un flessus des coudes et des interphalangiennes ; le cadet est en scolarité adaptée et présente une ataxie. Des anomalies associées sont présentes : anomalies vertébrales et des membres, communication inter ventriculaire chez l'ainé, kyste cortical rénal chez le cadet.

L'analyse génétique par exome réalisé dans la famille a permis d'identifier un nouveau variant pathogène (p.Met1Thr) du gène CCDC22 situé sur le chromosome X, hémizyote chez les 2 garçons, transmis par la mère hétérozygote.

Notre observation précise le phénotype et élargit le spectre des mutations CCDC22. Les mutations dans ce gène ont été identifiées récemment par séquençage d'exome et par transcriptome sur des cohortes de patients présentant une déficience intellectuelle liée à l'X. Comme les nôtres, ces enfants présentent un syndrome de DW syndromique avec des signes associés proche du syndrome de Ritscher Schinzel (OMIM 220210) ou syndrome 3C.



## MAUVAISE TOLÉRANCE À L'INTRODUCTION D'UN RÉGIME CÉTOGÈNE POUR SUSPICION DE DÉFICIT EN PDH : ÉVOQUONS UN AUTRE DIAGNOSTIC ?

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Le régime cétogène est un traitement proposé dans le déficit en PDH, privilégiant la bêta-oxydation comme source énergétique.

Nous rapportons un patient de 9 mois avec dégradation rapide dès 3 mois de vie : hypotonie majeure, absence de contact et cardiomyopathie hypertrophique. L'IRM cérébrale montrait des hypersignaux T2 des globes pales et une hypomyélinisation. Le lactate et le pyruvate étant élevés (sang, LCR) avec un rapport  $<20$ , le déficit en PDH évoqué était confirmé par l'activité enzymatique effondrée. Les CAA sanguine, CAO urinaire et profil des acylcarnitines plasmatiques étaient normaux. L'introduction du régime cétogène se compliquait d'emblée d'un coma acidocétosique sans hyperlactatémie avec cétonurie majeure. Amélioration rapide après apport glucidique et hydratation. L'étude génétique de la PDH ne montrant pas d'anomalie, devant ce tableau atypique pour un déficit primaire en PDH un panel de gènes de pathologies neurométaboliques était testé, montrant une mutation homozygote dans le gène ECHS1.

Le déficit en SCEH (Short Chain Enoyl-CoA Hydratase, gène ECHS1) induit un phénotype variable associant encéphalopathie, épilepsie, surdité, atrophie optique, cardiomyopathie. SCEH catalyse l'hydratation réversible du méthacrylyl-CoA au niveau du métabolisme de la valine, potentiellement toxique, et l'hydratation des chaînes courtes d'hydroxyacyl-CoA au niveau de la bêta-oxydation. L'accumulation de produits toxiques serait responsable des déficits secondaires observés comme le déficit en PDH. Deux cas de mauvaise tolérance au régime cétogène ont été décrits comme chez notre patient.

Devant un tableau clinique et biologique compatible avec un déficit primaire en PDH, la mauvaise tolérance d'un régime cétogène doit faire évoquer cette cause rare de déficit secondaire, le déficit en SCEH.

## PHENOTYPIC AND GENOTYPIC FEATURES OF A POPULATION OF PATIENTS WITH AUTISM SPECTRUM DISORDERS

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### Study objectives:

Autism Spectrum Disorders (ASD) are a group of neurodevelopmental disorders characterized by persistent deficits in social communication and social interaction across multiple contexts and presence of restricted, repetitive patterns of behavior, interests, or activities. Autism is characterized by both phenotypic and genetic heterogeneity and, so far, hundreds of genes and loci have been identified. Several studies have highlighted the contribution of the Copy Number Variants (CNVs) to the pathogenesis of autism. The aim of the study was to describe phenotypic and genotypic features of individuals with ASD and particularly to use Chromosomal Microarray (CMA) to investigate the presence of CNVs. Furthermore we tried to compare the distribution of some phenotypic features (gender, cognitive level, language difficulties, dysmorphism, congenital malformation, epilepsy, MRI and EEG abnormalities, parental neuropsychiatric conditions) among patients with CNVs versus those without CNVs.

### Methods:

We recruited 242 ASD patients underwent neuropsychiatric assessment, genetic examination, EEG and MRI. We performed CMA on a sample of 78 patients.

### Results:

Array-CGH detected CNVs in 17 patients (21,8%), 11 deletions and 17 duplications. Four patients carried more than one CNVs. We identified some loci that can be quite common in ASD population, such as 16p11.2, 1q21.1, 15q11-13, 22q11.2. We have also identified in five patients microdeletions and microduplications of distal 8p, supporting its contribution to ASD susceptibility. In our study only one patient had a CNV involving a gene that have been reported as ASD risk factors (CHRNA7); this gene play a role in synaptic plasticity, learning and memory. We didn't find any clinical and anamnestic clues that significantly correlate with pathologic array-CGH data. However among patients with CNVs there was a higher percentage of individual with intellectual disability and dysmorphic features or congenital malformations.

### Conclusions:

Our results confirm that Chromosomal Microarray is the first tier genetic test for the evaluation of people with ASD. It can be useful to have available detailed clinical criteria and stratify individuals based on their phenotype, in order to reduce genetic heterogeneity and improve statistical power of genetic analyses. A specific genetic diagnosis can enhance treatment of autistic patients and help in the genetic counseling.



**ÉPIDÉMIOLOGIE, CLASSIFICATION, NEUROPATHOLOGIE DES TUMEURS CÉRÉBRALES / EPIDEMIOLOGY, CLASSIFICATION, NEUROPATHOLOGY OF CEREBRAL TUMORS**

C. Godfraind (Paris, France)

The main advance of “the 2016 WHO Classification of Tumours of the Central Nervous System” is the addition of genetic markers allowing for “integrate diagnosis” of brain tumours. The diagnosis results from a combination between standard microscopic examination, immuno-histochemistry, and search for specific genetic alteration(s). The end-point is an improvement in tumour types identification, and also their sub-division. This will be further discussed and illustrated.

Gliomas are tumours that are either circumscribe or diffuse. This distinction is of major clinical impact, the former being mostly benign and the latter malignant. Radiological and histological analyses may help in this distinction. Genetic alterations are also useful, and amongst them BRAF and H3 mutations, as well as KIA1549-BRAF fusion. This latter fusion is associated with circumscribed lesions, and mainly, pilocytic astrocytomas. These tumours may also bear BRAF mutation, a genetic alteration shared with other brain tumours, generally circumscribed as gangliogliomas. Meanwhile ones has to be caution. Indeed, BRAF mutations have also been reported in diffuse glioma, including glioblastoma. Such consideration illustrates why final diagnosis of brain tumours has to be set up on combine histology and genetic considerations.

Also, histone mutations (H3) that were first described in children are indicative of diffuse gliomas. Interestingly there are two main mutations: H3-K27M and H3-G34R/V. The former is related to midline lesions, including pontine glioma, while the latter is linked to hemispheric diffuse gliomas. Diffuse gliomas of teenagers and young adults have an intermediate position while considering their genetic status. Indeed, they share either mutations associated with childhood diffuse gliomas (H3), or with adult ones (IDH1/2).

Genetic considerations have also largely improved medulloblastomas subdivision. Those posterior fossa tumours, mostly affecting children, are now classified according to histological features but also to genetic characteristics. The latter can be partly transcribed at histological level using immuno-histochemistry, and so allow for histological recognition of three out of the four genetic medulloblastomas sub-groups: SHH sub-group, WNT sub-group and a third sub-group combining of the genetically group 3 and 4.

Meanwhile the improvements owe by the 2016 classification, they are still brain tumours unclassified. High-throughput genetic analyses, including methylome analyses, help for further classification of those lesions, and to identify new entities. This will be illustrated.

Not infrequently painters reinterpret old masters giving rise to new emotions. Nowadays, neuropathologists add genetic to their diagnostic palette permitting more accurate diagnosis, and such hopes for development of more efficient treatments.

**TUMEURS DU SNC : DIAGNOSTIC ET APPROCHES THÉRAPEUTIQUES / CNS  
TUMORS: DIAGNOSIS AND THERAPEUTIC APPROACHES**

F. Fagioli (Torino, Italy)

Central nervous system (CNS) neoplasms are the second most common group of tumors in children, second only to leukemia. Despite advances in neuroradiology, neurosurgery, radiotherapy and chemotherapy over the last two decades, survival still does not exceed 65-70%, having improved notably only for medulloblastoma (5-years overall survival of 80% for standard-risk patients). High-grade gliomas, metastatic or recurrent medulloblastoma, rare embryonal tumors (e.g. AT/RT, ETMR) and diffuse intrinsic pontine gliomas (DIPG) are still challenging diseases with an unsatisfactory prognosis.

The signs and symptoms in children with CNS at diagnosis depend on the type and location of the tumor, the presence of hydrocephalus or increased intracranial pressure, and the age of the child. In infants, some non-specific symptoms, such as irritability and vomiting, are often misdiagnosed, since they are often present in several other non-neoplastic common conditions of infancy. Visual loss, usually promptly diagnosed in adolescents and adults, is sometimes recognized with delay in very young children. Indeed, a detailed history and neurologic examination is often fundamental in achieving a prompt diagnosis in children with intracranial neoplasms. Diagnosis is confirmed by imaging (computed tomography and magnetic resonance imaging). Lumbar puncture and / or dosage of tumor markers may be useful in some specific cases.

Neurosurgery is often the first therapeutic step in children with CNS tumors. Although in some cases it can be curative (e.g. cerebellar low-grade glioma), chemotherapy and / or radiotherapy (local or craniospinal) are often essential for the treatment. Clinical presentation and neuroradiology imaging still represent the mainstays of diagnosis, while neurosurgery, chemo- and radiotherapy are the strongholds of treatment.

Nonetheless, novel technologies have been improving our understanding of the genetic and the molecular basis of pediatric brain tumors, and are today integrating traditional pathology in the diagnostic phase. The recently published World Health Organization Classification of Tumors of the Central Nervous System (2016), for the first time, uses molecular parameters in addition to histology to define many tumor entities, thus defining new diagnostic concepts for CNS tumors in the molecular era. Furthermore, such advancements in molecular biology and genetics have been providing promising tools in the field of treatment: genomic profiling studies of medulloblastoma, ependymoma, and DIPG have redefined therapeutic stratification of patients with these tumors, showing that genotypic information may be linked to the clinical course. Potentially actionable targets have been identified, and might provide powerful therapeutic tools that will soon integrate and improve the treatment of children and adolescents with CNS tumors.



## GENETIC ASPECTS IN THE WORK-UP OF CEREBRAL TUMORS

V.Bours (Liège, Belgique)

Cancers in children are rare diseases and genetic predisposition plays a significant role in a large proportion of patients. Several genetic syndromes are indeed associated with a risk of brain tumors and large studies indicated that close to 10% of pediatric CNS tumors are associated with such syndromes, for instance the Li-Fraumeni syndrome, NF1 and NF2, FAP, CMMRD, Gorlin syndrome... However, some reports also suggest that, by searching widely for cancer predisposition, we might observe fortuitous associations.

The identification of familial cancer risk is important to orient the treatment and to propose the appropriate surveillance for the patient and his family. Some criteria should be considered as risk factors for cancer syndromes and lead to a genetic counseling. These criteria are linked with the patient clinical presentation (histology of the tumor, bilateral or multifocal tumors, associated clinical features, age at diagnosis) and of course with the family history. However, due to incomplete penetrance and de novo mutations, a family history is absent in a significant number of cases.

In summary, a careful clinical examination and a familial history are required for every CNS pediatric tumor. In case of doubt, the opinion of a geneticist should be requested.

# C4

## **EVOLUTION OF THE ROLE OF NEUROSURGERY IN THE TREATMENT OF CEREBRAL NEOPLASIA PEDIATRIC NEUROSURGERY, CHILDREN HOSPITAL REGINA MARGHERITA**

P. Peretta (Torino, Italy)

The role of neurosurgery in the treatment of cerebral neoplasia has become more and more determinant over the last years.

Technological advances significantly improved the patient's treatment and follow-up.

Neuroimaging allows us to perform a correct diagnosis and to understand the relationship between the tumor and eloquent areas. Functional MRI is essential for patients with a neoplastic lesion in eloquent areas.

Therefore, a careful preoperative evaluation of the patient is required before any surgical approach and then an accurate planning of the correct surgical route is also mandatory.

The neuronavigation is an essential instrument that lets us process the images in the operating room during surgery. The neurosurgeon has the chance to plan the correct approach, avoiding dangerous areas and to know his position during the operation.

MRI and CT scans can be performed intraoperatively to check if the tumor removal is complete or not.

Recently, the role of intraoperative ultrasound has been studied to control the quality of tumor removal and it is a very promising technology.

In the last two decades the intraoperative monitoring completely changed the surgical approach to CNS tumors and consequently their follow-up. This technique allows us to monitor the neurological functions during the operation and to map, for example, the floor of the fourth ventricle in case of medulla oblongata tumors. It is now possible to remove tumors that were impossible to approach in the past. A total or subtotal removal gives a better prognosis and in some cases a complete recovery from the neoplasia.

Unfortunately there are some lesions which are still not operable, i.e. pons tumors. New strategies are necessary to handle these diseases.



**RADIO- ET PROTONTHÉRAPIES, TOXICITÉ TARDIVE DES TRAITEMENTS  
RADIO- AND PROTONTHERAPIES, LATE TOXICITY OF THE TREATMENTS**

F.Fagioli, A.Mussano, (Torino, Italy)

Recent progress in the treatment for pediatric malignancies using a combination of surgery, chemotherapy, and radiotherapy has improved survival.

However, late toxicities of radiotherapy are a concern in long-term survivors. Irreversible, long-term side effects of conventional radiation therapy for pediatric cancers have been well documented and include growth disorders, neurocognitive toxicity, ototoxicity with subsequent effects on learning and language development, renal, endocrine and gonadal dysfunctions.

Radiation-induced secondary malignancies have also been reported as possible very severe adverse effects.

The energy of X- rays commonly used for the treatment of pediatric malignancies reaches a peak at a certain depth and then gradually declines along the irradiation pathway.

Therefore, some normal tissue close to the target tumor receives a high dose. Modern techniques of irradiation, like Intensity-modulated radiotherapy (IMRT), better conforming the beam delivery to the target volume, have achieved the goal of reducing the dose to surrounding tissues. However, the lower dose area is increased with these techniques and this leads to a significant risk of secondary cancer.

In contrast, proton beams have a sharp Bragg peak, with low energy before the peak and almost zero energy after the peak. Therefore, in proton beam therapy (PBT), normal tissue around the tumor receives a reduced dose compared to photon radiotherapy, and this is especially beneficial for pediatric tumors or tumors adjacent to normal tissue for which irradiation should be strictly avoided.

In PBT, the tumor control rate is similar to that in photon radiotherapy, but late toxicity and the secondary cancer risk should be much lower due to the dose distribution.

For this reason, PBT has potential as a treatment for pediatric tumors, but fewer institutions have proton beam centers compared to those in which normal photon radiotherapy is available.

Our presentation reviews the toxicity and late effects data concerning pediatric central nervous system tumors; furthermore it describes, for each type of pediatric brain tumors, the present challenges, the contribution of radiotherapy as a treatment component and the possibilities to improve it, including the use of particle therapy and its assessment by an evidence-based medicine approach.

# C6

## CURRENT PLACE OF CHEMOTHERAPY IN THE TREATMENT OF PEDIATRIC BRAIN TUMORS

D. Frappaz (Lyon, France)

Brain tumors were considered as chemoresistant for a long period, due to the concept of brain blood barrier resistance. Only lipophilic drugs such as nitrosoureas were supposed to be effective. However, in tumor tissue, this barrier is often disrupted and clinical evidence shows that most chemotherapy compounds penetrate the parenchyma. It is now part of the tools that may be used to treat brain tumors.

It may be used as standard dose, as high dose with stem cell support, or as low dose metronomic strategies. It may be used orally, intra venously, intra thecally.

It is currently used either alone, or in combination with surgery and radiation therapy (and very probably immunotherapy and targeted therapies in the close future). As radiation therapy has deleterious effects in children, chemotherapy is often used to delay or abolish the need for radiation. In medulloblastoma, chemotherapy may be the only additional strategy after surgery in infants and young children with good prognostic features; for older children, it is used to decrease the dose of radiation delivered to supratentorial region during craniospinal radiation. In low grade gliomas, one or several lines of exclusive chemotherapy may successively be used; in high grade gliomas, chemotherapy is only an adjuvant therapy to radiation therapy; in germ cell tumors, chemotherapy may help to limit the fields of radiation therapy; in ependymoma, the place of chemotherapy is debated and deserves randomized trials in both sides of the Atlantic Ocean.

The toxicities of chemotherapies are not only on hematopoietic system, but may also involve neurological, renal, auditory complications among others

As chemotherapy is one of the tools, its use should come from a multidisciplinary discussion, followed by a discussion on risk benefits with parents and children when feasible.





**CNS TUMORS AND EPILEPSY: CLINICAL AND NEUROPHYSIOLOGICAL ASPECTS**

P. Vigliano (Torino, Italy)

Brain tumors have an incidence of 1-3 per 100,000 children.

In association with malformations of cortical development, hippocampal sclerosis and ischemic damage, the tumors are one of the most common identifiable causes of drug-resistant epilepsy and, after cortical dysplasias, they represent the second most common finding in series of patients treated with neurosurgery for focal epilepsy.

In children, benign tumors associated with epilepsy account for 2-5% of CNS tumors; they are predominantly supratentorial, significantly more frequent in infants under 4 years of age. Grade I° glioneural tumors represent just over 50% of tumors responsible of epilepsy which appears to be intractable in a great percentage of cases. Focal seizures, of simple and complex type, are the most common clinical manifestation.

Studies on adult patients with tumoral epilepsy show that currently available antiepileptic drugs have little to no influence on the known epileptogenic mechanisms, and that could contribute to their poor efficacy. The role of the tumor on epileptogenicity has not yet been fully elucidated; studies in animal models and in adult patients show that, in the glial tumor, mechanical and biochemical factors affect the peritumoral network favoring excitatory mechanisms and the onset of epileptic activity that progresses over time.

In children focal epilepsy may be the only sign of a benign tumor and is sometimes the epilepsy itself that affects the quality life of the patients. A benign tumor placed in a region of difficult surgical approach and that interferes with the brain function can be «malignant» for life and patient's development. Currently different neurosurgical techniques can afford a normal life expectancy even in the difficult situations (e.g.: the disconnection techniques in the forms of gelastic epilepsy caused by hypothalamic hamartoma).

A total surgical excision of the tumor allows the healing of epilepsy in 84% of young patients; if the lesion is located in the temporal lobe, the healing expectancy reaches 92%.

The histological diagnosis of different subtypes of cancer is very important, but it is sometimes very difficult and varies from center to center, since there is no consensus on histological criteria for the classification of benign tumors; the proportion of tumor cells can also vary within the same tumor and in approximately 1/3 of cases an association with other cortical malformations is observed. Even the classification of the degree of the WHO cancer can be uncertain. So it can be difficult to determine the extent of neurosurgical resection of the epileptogenic lesion.

The electroencephalographic data currently have a lower importance in the diagnosis of tumors than in the past, however the morphology of the electroencephalographic abnormalities (slow or paroxysmal) is useful in the localization of the epileptogenic foci - in association with invasive investigations such as the study with depth electrodes or subdural grids during neurosurgical intervention - and allow to establish the area of resection.

Recent genetic studies on resection pieces can be used to help in the categorization of tumors and in the decision to give post-surgical radiotherapy and/or chemotherapy and the timing of follow-up.

**AUTOIMMUNE ENCEPHALITIS DUE TO NEURAL ANTIBODIES: DIAGNOSTIC APPROACH**

C. Bien (Bielefeld, Germany)

The concept of autoimmune encephalitis due to neural antibodies was detected and developed in adult patients. The key step was the discovery of antibodies against neurons. In the 1980s/1990s, intracellular antigens were identified, namely glutamic acid decarboxylase (GAD) and the onconeural antigens (Hu, Ma and so on). The discovery of antibody targets on neural surfaces in the last ten years or so was a major breakthrough in neurology. Frequently encountered antibodies are directed against the N-methyl-D-aspartate receptor (NMDAR), leucine-rich glioma inactivated protein 1 (LGI1), and  $\gamma$ -aminobutyric acid-B receptor (GABABR). Diagnostics for these antibodies is attractive because they are highly specific, they explain the pathophysiology of the conditions, and they predict a good response to immunotherapy.

The role of these antibodies in children and adults is becoming more transparent. A large proportion of anti-NMDAR encephalitides is diagnosed in girls (less frequently in boys). Other antibodies, e.g. against LGI1, GABABR or onconeural antibodies (against Hu, Ma), are found mainly in adults but should be considered in the differential diagnosis of pediatric acute and subacute encephalitic presentations, too. Selection criteria for testing of patients should provide an ideal balance between specificity and sensitivity. Such criteria still need to be defined. Typical features of patients with neural antibodies are multifocal encephalopathies with psychiatric and epileptic manifestations, post-viral secondary autoimmune encephalitides, and limbic encephalitis. A time and cost effective diagnostic procedure is multiparametric testing for a broad battery of antigens. In patients with specific antibodies, immunotherapy is recommended; onconeural antibodies should prompt tumour search.



**AUTOIMMUNE ENCEPHALITIS DUE TO NEURAL ANTIBODIES: THERAPEUTIC APPROACH**

T. Granata (Milano, Italy)

Autoimmune encephalitides in children are a growing group of treatable antibody-mediated disorders with favorable evolution in most cases. The treatment includes immunotherapy (and, in a minority of pediatric patients, tumor removal) as well as the symptomatic treatment of epileptic seizures, movement disorders, insomnia, and psychiatric symptoms which may be variably associated in a single patient. Guidelines for immunotherapy are still lacking, and controlled trials are necessary to establish the best initial therapies, the duration of treatment in responders, the appropriate time to wait before moving to second-line treatment, and finally the potential effect of second line treatment, also in responders, to prevent relapses. Despite these limitations, most groups consider as first line treatment the use of high-dose steroids associated with IVIg or plasmapheresis; so far there is not convincing evidence of superiority for either approach. Patients who do not benefit from first line therapy, should enter a second line therapy with immunosuppressive drugs, either rituximab or cyclophosphamide, and again there are no data supporting the superiority for either approach. The management of the several symptoms first requires their accurate recognition, definition and assessment, and the knowledge of potential side effects of antiepileptic and psychotropic drugs which could either mimic or worsen symptoms of encephalitis.

## INTERFÉRONOPATHIES À L'ORIGINE DES ATTEINTES INFLAMMATOIRES CÉRÉBRALES : ASPECTS CLINIQUES / INTERFERONOPATHIES CAUSING CEREBRAL INFLAMMATORY LESIONS: CLINICAL ASPECTS

Simona Orcesi (Pavia, Italy), Elisa Fazzi (Brescia, Italy)

Type I interferons (IFN) are cytokines that are among the cell's first lines of defence against pathogens.

A new class of Mendelian inherited disorders, linked to defective regulation of type I IFN, has recently been described. The type I interferonopathies are characterized by evidence of persistent up-regulation of type I interferon signalling, assessed by measuring the expression of interferon-stimulated genes (ISGs), and they currently include at least 18 genotypes; most of the mutated genes are involved in the metabolism or recognition of nucleic acids.

Many type I interferonopathies involve the central nervous system (CNS) and cause cerebral inflammatory lesions. Key clinical signs include CNS involvement (intracranial calcification), vasculitic/chilblain-like skin lesions, recurrent fever, interstitial lung disease and lupus-like disease.

Although Aicardi-Goutières syndrome (AGS), first described in 1984, is the prototypical type I interferonopathy, this family of disorders is increasing and has a remarkably broad spectrum of neurological phenotypes.

It is now recognized that mutations in seven genes (AGS1-7) may result in the classical AGS phenotype, whose clinical and radiological features are an early-onset, severe neurological disorder with intracranial calcification, leukoencephalopathy, cerebral atrophy, progressive microcephaly associated with cerebrospinal fluid (CSF) pleocytosis, elevated CSF interferon activity, and, in most patients, increased expression of ISGs in peripheral blood (the "interferon signature").

The clinical symptoms appear during the first months of life. Irritability, crying and recurrent episodes of sterile pyrexia, indicating the onset of a sub-acute encephalopathy, are followed by an increasing psychomotor delay and/or a loss of early acquired skills, as well as signs of neurological impairment, pyramidal and extrapyramidal signs and slowing of head growth. After a few months, the clinical picture typically stabilises and no further progression of the disease is detectable. Skin lesions, usually chilblains, are an important feature of mutations in AGS1-7. Glaucoma can also be present, as can features of autoimmunity, most commonly thyroiditis, and less frequently lupus-like disease.

The disease trigger is not known, and neither it is understood why, after several months, the clinical picture stabilises. Generally speaking, the clinical picture depends on the timing of the interferon-related insult, and it may also be associated with exposure to environmental triggers, such as infection, and with the effect of genetic modifiers. Consequently there are also different clinical types: "prenatal/neonatal onset AGS" and "later onset AGS".

Moreover, children with mutations in SAMHD1 (AGS5) are at increased risk of developing cerebrovascular disorders.

Bilateral striatal necrosis (BSN) resulting in severe dystonic-rigid clinical features is, instead, the distinctive phenotype in AGS patients with mutated ADAR1, in whom the onset can occur even after the first year of life.

Finally, patients with "idiopathic spastic paraparesis" (lower limb involvement only, normal intelligence, normal brain MRI, and positive interferon signature in only some cases) can have mutations in AGS genes, specifically ADAR1, IFIH1 and RNASEH2B. The fact that these genetic mutations can result in clinical pictures not necessarily classifiable as AGS strengthens the suggestion that there exist factors, as yet unknown and probably genetic, capable of modifying the effect of AGS gene mutations.



# C11

## **INTERFERONOPATHIES CAUSING CEREBRAL INFLAMMATORY LESIONS: GENETIC AND MOLECULAR ASPECTS MIN AE LEE-KIRSCH**

M.A. Lee-Kirsch (Dresda, Germany)

Type 1 interferonopathies represent a group of genetically determined rare diseases caused by defects of the innate immune system. Central to all type 1 interferonopathies is a dysregulation of the antiviral type 1 interferon (IFN) axis, which results in constitutive overproduction of type 1 IFN. All type 1 interferonopathies present as systemic inflammatory disorders characterized by autoinflammation and autoimmunity. Although the clinical spectrum is highly variable and broad, neurological and cutaneous manifestations represent the most salient findings. The prototypic type 1 interferonopathy is Aicardi-Goutières syndrome, which manifests in early childhood as encephalopathy with dystonia, seizures and fever episodes. Mutations in at least 7 distinct genes have been identified in patients with AGS. Understanding their molecular functions has provided novel insight into disease pathways leading to autoinflammation and autoimmunity. Thus, chronic type 1 IFN activation is due to defects in pathways affecting the metabolism or the immune recognition of intracellular nucleic acids. Our current understanding of the molecular mechanisms underlying type 1 interferonopathies indicates that an immunomodulatory intervention targeting the type 1 IFN axis might be of therapeutic value.

# C12

## NEUROLOGICAL DISORDERS ASSOCIATED WITH STRIATAL LESIONS: CLASSIFICATION AND DIAGNOSTIC APPROACH

D. Tonduci (Milan, Italy)

Neostriatal abnormalities can be observed in a very large number of neurological conditions clinically dominated by the presence of movement disorders. The neuroradiological picture in some cases has been described as "Bilateral Striatal Necrosis" (BSN). BSN represents a condition histo-pathologically defined by the involvement of the neostriata and characterized by initial swelling of putamina and caudates followed by degeneration and cellular necrosis. After the first description in 1975 numerous acquired and hereditary conditions have been associated with the presence of BSN. At the same time, a large number of disorders involving neostriata have been described as BSN, in some cases irrespective of the presence of signs of cavitation on MRI. As a consequence, the etiological spectrum and the nosographic boundaries of the syndrome have progressively become less clear.

In this presentation we will review the clinical and radiological features of the conditions associated with MRI evidence of bilateral striatal lesions. Based on MRI findings we distinguished two groups of disorders: BSN and other NeoStriatal Lesions (SL). This distinction is extremely helpful in narrowing the differential diagnosis to a small group of known conditions. The clinical picture and complementary exams can finally lead to the diagnosis.



## DIAGNOSTICS OF DYSTONIA IN THE NEXT GENERATION SEQUENCING ERA

G. Collob-Bérout (Marseille, France), David Salgado (Marseille, France), Jean-Pierre Desvignes (Marseille, France), Christophe Bérout (Marseille, France)

Dystonia is a movement disorder characterized by involuntary, sustained and patterned contractions of group of muscles, leading to twisting movements and/or abnormal postures.

Any region of the body may be affected, alone or in various combinations. In addition to the widely varying clinical manifestations of dystonia, there is also a great genetic heterogeneity with often overlapping clinical phenotypes. The last recommendation for the nomenclature of genetic disorders reported more than 40 genes for dystonia highlighting the great challenge to focus on specific genes for molecular diagnosis. This extensive genetic heterogeneity is thus a major concern for molecular diagnosis and genetic counselling.

Various strategies have been recently proposed to optimize mutation detection with next-generation DNA sequencing (NGS). Since 2005, NGS platforms have been implemented largely leading to reduced DNA sequencing cost by four orders of magnitude relative to Sanger sequencing. Consequently, clinical use of targeted sequencing, whole exome sequencing (WES) or whole-genome sequencing (WGS) is increasing. This cost-effective option is becoming the technique of choice in the work-up of disorders that involve multiple genes and proves its effectiveness in the identification of genes involved in previously undiagnosed cases (near 25%).

If the overall detection rate of a causative mutation is today low, this may strongly benefit from NGS. However, some limitations exist: technical issues, bioinformatics pipelines, and lack of knowledge for many genes. The specific challenge is thus the NGS data interpretation and identification of new disease-causing mutations/genes.

## ABNORMAL MOVEMENTS IN TREATABLE METABOLIC DISEASES

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There are a number of inherited metabolic disorders causing movement disorders in childhood that can be modified with specific therapeutic interventions. In children with dystonia, it is of utmost importance to perform a therapeutic trial with levodopa, and to perform a metabolic screening to rule out other treatable conditions such as Glut-1 deficiency, Wilson disease, cerebral creatine deficiency and other defects in intermediate metabolism, such as organic acidurias.

Recently, a growing number of key proteins that are essential for the transport of vitamins and trace elements through cell membranes have been described; some of these disorders present in normal developing children with acute onset dystonia and basal ganglia injury, responding extremely well to the oral supplementation of vitamins or to specific chelation therapy.

Genetic defects in thiamine transport and metabolism are recessively inherited disorders presenting in childhood, adolescence and early adulthood. Well-defined clinical phenotypes have been recognized in the following defects: (1) SLC19A2 (thiamine transporter-1) causes Roger's syndrome or thiamine responsive megaloblastic anemia; SLC19A3 (thiamine transporter-2) is responsible for biotin thiamine responsive basal ganglia disease, Leigh syndrome (LS), infantile spasms with lactic acidosis, and Wernicke encephalopathy-like syndrome; (3) TPK1 (thiamine phosphokinase) causes LS; and finally (4) SLC25A19 (mitochondrial thiamine pyrophosphate carrier) produces Amish microcephaly and bilateral striatal degeneration and progressive polyneuropathy.

In contrast to mitochondrial disorders leading to Leigh syndrome, thiamine supplementation in patients with SLC19A3, TPK1 and SLC25A19 defects presenting with encephalopathy, generalized dystonia, and basal ganglia lesions, leads to metabolic stability, reduced dystonia and disability, and better survival curve. Thus, it is essential for clinicians to suspect these disorders in order to make an early diagnosis and accurate treatment.

Mn dyshomeostasis may result from inherited genetic defects in one of the transporters implicated in Mn homeostasis, namely SLC39A8, SLC30A10 and SLC39A14. Patients with recessive mutations in SLC30A10 and SLC39A14 show a progressive dystonia-parkinsonism syndrome, hypermanganesemia and Mn deposition in the basal ganglia. It has been postulated that both SLC30A10 and SLC39A14 act in partnership for efficient hepatic Mn detoxification, and that cerebral Mn deposition is a consequence of the increased systemic Mn load. Chelation therapy in both disorders increases Mn urinary excretion and decreases plasma Mn concentrations, with variable clinical improvement.

In summary, in children with acute or subacute dystonia and basal ganglia lesions, we must consider recently described treatable defects, such as genetic defects in the transport and metabolism of vitamins (e.g. thiamine and biotin) and metals (e.g. manganese and copper). Early recognition followed by prompt therapeutic intervention of these disorders may improve the neurological outcome, thus, the identification of potential biomarkers is a major goal of research.



## DYSKINÉSIES PAROXYSTIQUES : AN UPDATE

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Les dyskinésies paroxystiques (DP) sont des épisodes de mouvements choréoathétosiques/ dystonique à début et fin brusques sans altération de la conscience, de durée variable allant de quelques secondes à plusieurs heures. Les vidéos sont très utiles au diagnostic clinique. L'état intercritique peut être normal ou altéré. Nous rapportons une mise à jour des différentes caractéristiques cliniques, génétiques, physiopathologiques et thérapeutiques.

Ces DP peuvent être secondaires à des lésions cérébrales (inflammatoire (SEP), vasculaires, traumatiques) justifiant l'IRM cérébrale ou à des désordres endocriniens ; mais elles sont le plus souvent d'origine génétique primitive ou neurométabolique. La classification avant les découvertes génétiques était basée sur des critères cliniques tenant compte de la durée des épisodes et les facteurs déclenchants permettant de distinguer les dyskinésies paroxystiques kinésigéniques DPK (déclenchées par les changements de position), non kinésigéniques (DPNK), induites par l'exercice (PED) et hypnagogiques (Bruno et al 2004). Depuis les avancées génétiques, émerge une nouvelle classification tenant compte de ces mêmes critères cliniques et des gènes en cause dont le nombre ne cesse de croître : PRRT2 (gène majoritaire des DPK), SCL2A1, ADCY5, PKND, PDHA1, PDHX, ATP1A3, SCN8A...).

Dans certains cas, en fonction des données cliniques et familiales, le diagnostic génétique peut être évoqué, et une thérapeutique proposée. Cependant un phénotype clinique peut être en rapport avec plusieurs anomalies génétiques et inversement une anomalie génétique peut être responsable de plusieurs phénotypes. Du fait de cette absence stricte de corrélation phénotype/génotype, le diagnostic peut parfois être difficile et justifier des investigations (IRM cérébrale, examens biologiques, analyse du LCR en fonction du contexte); Et l'analyse de panels de gènes de DP maintenant proposé, peut permettre d'accéder à un diagnostic moléculaire dont l'identification souligne la variété des processus physiopathologiques.

# C16

## UPDATE ABOUT RECENT PROGRESS IN BASAL GANGLIA DISORDERS IN CHILDREN

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Recent advances in genetic technologies has expended the identification of movement disorders genetic causes. The impact of these discoveries is huge; in one hand, sometimes it jeopardizes the previously established movement disorders classification and nomenclature; on the other hand, it provides clues for common physiopathological mechanisms for disorders characterized by different spectrum of clinical manifestations, which were previously considered as very distinct. Finally, these new tools may help the clinician in his therapeutic strategy, and provide the geneticist with relevant clues for familial genetic counseling.

These concepts will be illustrated by presentation of a patient with GNAO1 mutation; this gene has recently been involved in an early-onset choreo-dystonic syndrome with or without epileptic encephalopathy. The case of a patient with KMT2B mutation, responsible of early-onset dystonia, will also be discussed.



