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BAHI-BUISSON N., EL SABBAGH S., SOUFFLET C., ESCANDE F., BODDAERT N., VALAYANNOPOULOS V., BELLANE-CHANTELOT C., LASCELLES K., DULAC O., PLOUIN P., de LONLAY P.

Myoclonic absence epilepsy with photosensitivity and a gain of function mutation in glutamate dehydrogenase.

Seizure - Eur. J. Epilep., 17 (7), 658-664, 2008

(Services cités : Métabolisme, Neurologie, U663, Explorations Fonctionnelles)

Activating mutations in glutamate dehydrogenase (GDH), de novo or dominantly inherited, are responsible for the hyperinsulinism/hyperammonemia (HI/HA) syndrome. Epilepsy has been frequently reported in association with mutations in GDH, but the epilepsy phenotype has not been clearly determined. Here, we describe a family with a dominantly inherited mutation in GDH. The mother, brother and both sisters had myoclonic absence seizures, but only the mother and one sister had the complete HI/HA pattern. For the two sisters with myoclonic absences, epilepsy started during the second year of life while the brother, it started at 6 years. All 3 children showed the same EEG pattern characterized by photosensitive generalized and irregular spike-wave discharges and runs of multiple spikes. The mother's EEG recordings were normal without photosensitivity. Magnetic resonance imaging (MRI) and spectroscopy (MRS) were normal. A direct effect of the GDH mutation, perhaps in combination with recurrent hypoglycemia and chronic hyperammonemia could provide a pathophysiological explanation for the epilepsy observed in this syndrome and these are discussed.

BAHI-BUISSON N., GUELLEC I., NABBOU R., GUET A., NGUYEN G., DULAC O., CHIRON C.

Parental view of epilepsy in Rett Syndrome.

Brain Dev., 30 (2), 126-130, 2008

(Services cités : Neurologie, U663)

Few instruments exist to measure the impact of epilepsy on the quality of life in Rett Syndrome (RS). Methods: We attended to describe seizures characteristics, parental opinion and quality of life related in RS by using a newly developed self administered questionnaire, postal sent to parents of French Association for Rett Syndrome (AFSR). Results: Two-hundred completed questionnaires were returned. Mean age of patients was 14.8+/-8.1years [3-42]. Parents reported that 70% of children had epileptic and non-epileptic seizures and mean age at first seizures was 7.3+/-5.1years [1-24]. No statistical difference was found between the ages of first seizures, diagnosis of epilepsy and introduction of treatment. Seizures had a negative impact on child and family's life (68% of cases), strongly correlated to the existence of generalized, prolonged, cyanotic and drug-resistant seizures, on the child's level of alertness and progress in communication skills and psycho-social consequences such as fear of seizures, and difficulties to find home care aids. Conclusions: We identified major concerns of parents with RS that determine the impact of seizures on children and their family's quality of life. Our results suggest that in order to improve seizures management in RS, better information should reduce fear about seizures and should improve the quality of life of RS.

BAHI-BUISSON N., GUTTIERREZ-DELICADO E., SOUFFLET C., RIO M., CORMIER-DAIRE V., LACOMBE D., HERON D., VERLOES A., ZUBERI S., BURGLLEN L., AFENJAR A., MOUTARD M.L., EDERY P., NOVELLI A., BERNARDINI L., DULAC O., NABOUT R., PLOUIN P., BATTAGLIA A.

Spectrum of epilepsy in terminal 1p36 deletion syndrome.

Epilepsia, 49 (3), 509-515, 2008

(Services cités : Explorations Fonctionnelles, Génétique Médicale Pédiatrique, Neurologie, U663)

Purpose: Previous reports have summarized the seizures types occurring in 1p36 deletion syndrome. To better define the spectrum of epilepsy, we studied 91 patients (median age 7.8 years) with confirmed 1p36 deletion. Methods: Based on clinical charts, we retrospectively analyzed the evolution of both the EEG findings and seizures. Results: Epilepsy occurred in 53 patients (58.2%), with onset at a median 2.75 months. First seizures were generalized tonic (8 cases), tonic and clonic (6) or myoclonic (12), simple partial (6), or complex partial (14). Thereafter, 20 patients (21.9%) developed infantile spasms with hypsarrhythmia, at a median age of 5 months. High doses of oral steroids were tried in nine cases, with a prompt remission of seizures in six. Among them, five were seizure-free at the time of evaluation. Conversely, two of three nonresponders to steroids developed severe and refractory epilepsy. At the time of evaluation, 32 patients were seizure-free, from a median age of 1.8 years. Nineteen patients (20.9%) had developed refractory epilepsy with polymorphic seizures, including generalized tonic and tonic-clonic seizures (13) combined with myoclonic seizures (11) and atypical absences (3), atonic seizures (2), or complex partial seizures (3). The EEG showed focal, multifocal or generalized spikes, polyspike, and waves, with poverty of the usual background rhythmic activities. Conclusions: Early epilepsy is a frequent finding in 1p36 deletion syndrome with infantile spasms as of the most common features that can contribute to a poor clinical outcome. Early diagnosis and management of infantile spasm in this condition is mandatory.

BAHI-BUISSON N., KAMINSKA A., BODDAERT N., RIO M., AFENJAR A., GERARD M., GIULIANO F., MOTTE J., HERON D., MOREL M.A., PLOUIN P., RICHELME C., DES PORTES V., DULAC O., PHILIPPE C., CHIRON C., NABOUT R., BIENVENU T.

The three stages of epilepsy in patients with CDKL5 mutations.

Epilepsia, 49 (6), 1027-1037, 2008

(Services cités : Explorations Fonctionnelles, Génétique Médicale Pédiatrique, Neurologie, Radiologie Pédiatrique, U663)

Mutations in the X-linked cyclin-dependent kinase-like 5 (CDKL5) gene are responsible for a severe encephalopathy with early epilepsy. So far, the electroclinical phenotype remains largely unknown and no clear genotype-phenotype correlations have been established. Purpose: To characterize the epilepsy associated with CDKL5 mutations and to look for a relationship between the genotype and the course of epilepsy. Methods: We retrospectively analyzed the electroclinical phenotypes of 12 patients aged from 2.5 to 19 years diagnosed with pathogenic CDKL5 mutations and one patient with a novel intronic sequence variation of uncertain pathogenicity and examined whether the severity of the epilepsy was linked to the type and location of mutations. Results: The epilepsy course reveals three successive stages: (Stage I) early epilepsy (onset 1-10 weeks) with normal interictal electroencephalogram (EEG) (10/13)

despite frequent convulsive seizures; (Stage II) epileptic encephalopathy with infantile spasms (8/8) and hypsarrhythmia (8/8). At the age of evaluation, seven patients were seizure free and six had developed refractory epilepsy (stage III) with tonic seizures and myoclonia (5/6). Interestingly, the patients carrying a CDKL5 mutations causing a truncation of the catalytic domain tended to develop a more frequent refractory epilepsy than patients with mutations located downstream (4/6, 66.6% versus 1/6, 16%) although, these trends are not yet significant. Discussion: Our data contribute to a better definition of the epileptic phenotype in CDKL5 mutations, and might give some clues to a potential relationship between the phenotype and the genotype in these patients.

BAHI-BUISSON N., NECTOUX J., ROSAS-VARGAS H., MILH M., BODDAERT N., GIRARD B., CANCES C., VILLE D., AFENJAR A., RIO M., HERON D., N'GUYEN-MOREL M.A., ARZIMANOGLU A., PHILIPPE C., JONVEAUX P., CHELLY J., BIENVENU T.

Key clinical features to identify girls with CDKL5 mutations.

Brain, 131 (10), 2647-2661, 2008

(Services cités : Génétique Médicale Pédiatrique, Neurologie, U663, Radiologie Pédiatrique)

Mutations in the human X-linked cyclin-dependent kinase-like 5 (CDKL5) gene have been shown to cause infantile spasms as well as Rett syndrome (RTT)-like phenotype. To date, less than 25 different mutations have been reported. So far, there are still little data on the key clinical diagnosis criteria and on the natural history of CDKL5-associated encephalopathy. We screened the entire coding region of CDKL5 for mutations in 183 females with encephalopathy with early seizures by denaturing high liquid performance chromatography and direct sequencing, and we identified in 20 unrelated girls, 18 different mutations including 7 novel mutations. These mutations were identified in eight patients with encephalopathy with RTT-like features, five with infantile spasms and seven with encephalopathy with refractory epilepsy. Early epilepsy with normal interictal EEG and severe hypotonia are the key clinical features in identifying patients likely to have CDKL5 mutations. Our study also indicates that these patients clearly exhibit some RTT features such as deceleration of head growth, stereotypies and hand apraxia and that these RTT features become more evident in older and ambulatory patients. However, some RTT signs are clearly absent such as the so called RTT disease profile (period of nearly normal development followed by regression with loss of acquired fine finger skill in early childhood and characteristic intensive eye communication) and the characteristic evolution of the RTT electroencephalogram. Interestingly, in addition to the overall stereotypical symptomatology (age of onset and evolution of the disease) resulting from CDKL5 mutations, atypical forms of CDKL5-related conditions have also been observed. Our data suggest that phenotypic heterogeneity does not correlate with the nature or the position of the mutations or with the pattern of X-chromosome inactivation, but most probably with the functional transcriptional and/or translational consequences of CDKL5 mutations. In conclusion, our report show that search for mutations in CDKL5 is indicated in girls with early onset of a severe intractable seizure disorder or infantile spasms with severe hypotonia, and in girls with RTT-like phenotype and early onset seizures, though, in our cohort, mutations in CDKL5 account for about 10% of the girls affected by these disorders.

BARNERIAS C., BODDAERT N., PASCALE G., ISABELLE D., HERTZ-PANNIER L., DULAC O., de LONLAY P., BAHI-BUISSON N.

Unusual magnetic resonance imaging features in Menkes disease.

Brain Dev., 30 (7), 489-492, 2008

(Services cités : U663, Neurologie, Radiologie Pédiatrique, Métabolisme)

We present a case of an inherited disorder of copper metabolism, Menkes disease in which MRI studies revealed the coexistence of T2 hypersignal in the temporal white matter with an increase of apparent diffusion coefficient indicative of vasogenic oedema combined with T2 hypersignal of the putamen and head of the caudate and decreased apparent diffusion coefficient indicative of cytotoxic oedema. These unusual MRI features emphasize the interest of newly developed techniques in early diagnosis in Menkes disease. The acute cerebral damage might result from the combined effects of acute metabolic stress due to infectious disease and prolonged status epilepticus, acting on a highly susceptible developing brain. Vasogenic oedema in the temporal white matter could be related to prolonged status epilepticus and vascular abnormalities. Cytotoxic oedema of the putamen and head caudate could result from energetic failure.

BAULAC S., GOURFINKEL-AN I., COUARCH P., DEPIENNE C., KAMINSKA A., DULAC O., BAULAC M., LEGUERN E., NABBOU R.

A novel locus for generalized epilepsy with febrile seizures plus in French families.

Arch. Neurol., 65 (7), 943-951, 2008

(Services cités : Neurologie, U663)

BACKGROUND: Generalized epilepsy with febrile seizures plus (GEFS(+)) is a familial autosomal dominant entity characterized by the association of febrile and afebrile seizures. Mutations in 3 genes--the sodium channel alpha1 subunit gene (SCN1A), the sodium channel beta1 subunit gene (SCN1B), and the gamma2 GABA receptor subunit gene (GABRG2)--and linkage to 2 other loci on 2p24 and 21q22 have been identified in families with GEFS(+), indicating genetic heterogeneity. **OBJECTIVES:** To localize by means of linkage analysis a new gene for GEFS(+) in a large family with 11 affected members and to test the new locus in 4 additional families with GEFS(+). **DESIGN:** Family-based linkage analysis. **SETTING:** University hospital. **PATIENTS:** Five French families with GEFS(+) and at least 7 available affected members with autosomal dominant transmission. All the patients had febrile seizures and/or afebrile generalized tonic-clonic seizures or absence epilepsy. **MAIN OUTCOME MEASURES:** We analyzed 380 microsatellite markers and conducted linkage analysis. **RESULTS:** In the largest family, a 10-cM-density genomewide scan revealed linkage to a 13-Mb (megabase) interval on chromosome 8p23-p21 with a maximum pairwise logarithm of odds (LOD) score of 3.00 (at Theta = 0) for markers D8S351 and D8S550 and a multipoint LOD score of 3.23. A second family with GEFS(+) was also possibly linked to chromosome 8p23-p21 and the region was narrowed to a 7.3-Mb candidate interval, flanked by markers D8S1706 and D8S549. We have not, so far, identified mutations in the coding exons of 6 candidate genes (MTMR9, MTMR7, CTSB, SGCZ, SG223, and ATP6V1B2) located in the genetic interval. **CONCLUSIONS:** We report a sixth locus for GEFS(+) on chromosome 8p23-p21. Because no ion channel genes are located in this interval, identification of the responsible gene will probably uncover a new mechanism of pathogenesis for GEFS(+).

BULTEAU C., DORFMULLER G., FOHLEN M., JALIN C., OLIVER M.V., DELALANDE O.

Epilepsy surgery during infancy and early childhood in France.

Neurochirurgie, 54 (3), 342-346, 2008

(Services cités : U663)

BACKGROUND AND PURPOSE: We present the epilepsy surgery activity in infants and children at the Fondation Rothschild Hospital, the main center dedicated to this activity in France. **METHOD:** A prospective study was conducted from 2003 to 2007 based on three populations: (1) children selected as candidates for surgery, (2) children undergoing presurgical evaluation and (3) children undergoing surgical procedures for epilepsy. **RESULTS:** Children selected as candidates for surgery: 304 children were referred and discussed by our multidisciplinary staff. They came from Paris and its suburbs (40%), the provinces (43%) or from other countries (14%). Sixty-one percent of them were included in our surgery program and 24% were excluded. Sixty-one percent of them were under 10 years of age. Children undergoing presurgical evaluation: 296 children were recorded: 140 EEG (47%), 46 with foramen ovale electrodes (16%) and 110 with invasive recording techniques (37%). Seventy percent of these children were under 10 years of age. Children undergoing surgical procedures: 316 children underwent surgery; 68% of them were under 10 years of age. The surgical procedures were focal resection (136 children), vertical parasagittal hemispherotomy (77 children), resection and or disconnection for hypothalamic hamartoma (69 children) and 34 had palliative surgery (callosotomy or vagal nerve stimulation). **CONCLUSION:** Eighty to 100 children undergo surgery each year in our department for drug-resistant partial epilepsy; 70% of them are less than 10 years of age. This activity is part of a network of pediatric neurologists who are deeply involved in treatment of severe epilepsy in children.

BULTEAU C., DORFMULLER G., FOHLEN M., JALIN C., OLIVER M.V., DELALANDE O.

Long-term outcome after hemispheric disconnection.

Neurochirurgie, 54 (3), 358-361, 2008

(Services cités : U663)

Hemispheric disconnection has been largely proposed for patients with severe epilepsy associated with a congenital or acquired hemispheric cerebral pathology. The classical procedure of anatomical hemispherectomy was progressively abandoned by neurosurgeons in order to avoid postoperative complications since then hemispherotomy techniques have been developed. Globally, with hemispheric disconnection, the rate of patients becoming seizure-free has been between 50 and 80%. The factors affecting seizure control have not been completely elucidated, but several authors suggested that differences in etiology as well as the hemispheric disconnection technique used may partially explain this variability. The percentage of seizure-free patients is higher with hemispherotomy techniques and in the group of patients with Rasmussen encephalitis, Sturge-Weber syndrome, and vascular insults. Depending on overall long-term progression, there is an improvement compared to preoperative status even if children exhibit heterogenous abilities. The lowest scores are observed for motor skills but communication and socialization are relatively well-preserved and strongly related to the duration of epilepsy: the longer the duration, the lower the scores were. Neuropsychological outcome following hemispheric disconnection makes it possible to study the development of hemispheric specialization during infancy and to provide information on cognitive recovery. Cerebral reorganization has been proved to exist in motor and language recovery. Ipsilateral corticospinal pathways seem to be involved in the movement of hemiplegic limbs. Everyday language can be supported by both hemispheres, but there is an early hemispheric specialization of the left

hemisphere according to metaphonologic abilities.

CHASSOUX F., CHIRON C.

Positron emission tomography: Which indications, which benefits ?

Neurochirurgie, 54 (3), 219-225, 2008

(Services cités : U663)

Positron emission tomography (PET) is currently used in the presurgical workup for drug-resistant partial epilepsies in addition to MRI. Interictal metabolism is studied in clinical practice using (18)fluoro-desoxy-glucose ((18)FDG). In medial temporal lobe epilepsy (MTLE) associated with hippocampal sclerosis, hypometabolism ipsilateral to the epileptogenic focus is found in 70-90% of cases. However, hypometabolism is larger than the structural lesion observed on MRI and includes the epileptogenic zone and ictal discharge spread areas. Hypometabolism is related to surgical outcome and cognitive disturbances in MTLE. Although the usefulness of PET appears less well-established in extratemporal lobe epilepsy and in children, its sensitivity may be improved by coregistration and superimposition of PET on MRI at any age. Focal hypometabolism can be easily detected by visual analysis, allowing detection of minor gyral abnormalities that may correspond to focal cortical dysplasias. Moreover, in cases of negative MRI, focal hypometabolism findings may help invasive monitoring planning and deep electrode placement for SEEG, and finally improve surgical outcome.

CHIRON C., DULAC O., PONS G.

Antiepileptic drug development in children : considerations for a revisited strategy.

Drugs, 68 (1), 17-25, 2008

(Services cités : Neurologie, U663)

The European Commission and the European Parliament have acknowledged the specific need for a proper evaluation of new drugs in children. The evaluation of the antiepileptic drugs (AEDs) available on the market illustrates the deficit in therapeutic trials for childhood epilepsy syndromes. Currently, the development of AEDs is mainly performed in children with focal epilepsy, whereas infants and the specific age-related epilepsy syndromes, particularly epileptic encephalopathies, are neglected. Infantile epilepsies remain 'therapeutic orphans', although they are the most frequent and deleterious disorders in the area of epilepsy. In order to circumvent the difficulties faced when conducting AED trials in children, we addressed the question of improving feasibility without decreasing quality, while optimally taking into account paediatric ethical requirements. For this review, we first raise the issues of paediatric epilepsies that require special considerations for randomized controlled trials (RCTs) in children. Then, we attempt to determine to what extent adult data could be extrapolated to children. Finally, we review innovative approaches that could be used in the evaluation of AEDs in children. The main specificities of paediatric epilepsies (heterogeneity, severity, cognitive impact, pharmacoresistance, syndrome-specific efficacy profile) are related to brain development and should be taken into consideration when establishing specific guidelines for the evaluation of AEDs in children. Extrapolating efficacy data from adults to children may be possible in focal epilepsy except in infants who need age-specific trials. Epileptic encephalopathies do not exist in adults and require specific trials. Pharmacokinetic data are required below a lower age limit for extrapolation of adult data to be determined in a case-to-case approach. Safety data are required at any paediatric age. RCTs in small but homogeneous populations in each paediatric-specific

epileptic syndrome, the use of sequential or responder-enrichment designs, and population pharmacokinetics represent potentially promising approaches to evaluate drugs in children in an efficient way.

CHIRON C., HERTZ-PANNIER L.

Structural and functional imaging: Particularities in children.

Neurochirurgie, 54 (3), 212-218, 2008

(Services cités : U663)

Surgery of partial epilepsies in childhood has largely benefited from the recent advances of imaging techniques, which carry a triple goal: (1) to contribute to the localization of the epilepsy onset zone, (2) to detect and delineate an underlying lesion, and (3) to study the spatial relationship between the epileptogenic zone and the neighboring functional cortex, in order to select patients and plan the resection. This noninvasive presurgical imaging workup must be compared to clinical and electrical data to estimate the postoperative prognosis, while invasive techniques such as SEEG, cortical stimulations, and IAT often remain indispensable in difficult cases, i.e., in cryptogenic epilepsies. As in adults, advances in MRI allow us to detect more and more subtle underlying lesions, but this requires repeating MR studies during early childhood and using adapted sequence parameters to account for ongoing myelination. Ictal SPECT and PET imaging prove especially useful in planning depth electrode placement when video-EEG is not contributive, when MRI looks normal or shows multiple abnormalities, or in cases of discrepant findings. Multimodal imaging greatly enhances the sensitivity of all of these techniques. Finally, functional MRI of motor and language functions provide noninvasive cortical mapping of essential functions, using age-adapted paradigms, in cooperating children from age five to six and from IQs around 60.

DESGUERRE I., NABBOUT R., DULAC O.

The management of infantile spasms.

Arch. Dis. Child., 93 (6), 462-463, 2008

(Services cités : Neurologie, U663)

DUBOIS J., DEHAENE-LAMBERTZ G., PERRIN M., MANGIN J.F., COINTEPAS Y., DUCHESNAY E., LE BIHAN D., HERTZ-PANNIER L.

Asynchrony of the early maturation of white matter bundles in healthy infants: Quantitative landmarks revealed noninvasively by diffusion tensor imaging.

Hum. Brain Map., 29 (1), 14-17, 2008

(Services cités : Radiologie Pédiatrique, U663)

Normal cognitive development in infants follows a well-known temporal sequence, which is assumed to be correlated with the structural maturation of underlying functional networks. Postmortem studies and, more recently, structural MR imaging studies have described qualitatively the heterogeneous spatio-temporal progression of white matter myelination. However, in vivo quantification of the maturation phases of fiber bundles is still lacking. We used noninvasive diffusion tensor MR imaging and tractography in twenty-three 1-4-month-old healthy infants to quantify the early maturation of the main cerebral fascicles. A specific

maturation model, based on the respective roles of different maturational processes on the diffusion phenomena, was designed to highlight asynchronous maturation across bundles by evaluating the time-course of mean diffusivity and anisotropy changes over the considered developmental period. Using an original approach, a progression of maturation in four relative stages was determined in each tract by estimating the maturation state and speed, from the diffusion indices over the infants group compared with an adults group on one hand, and in each tract compared with the average over bundles on the other hand. Results were coherent with, and extended previous findings in 8 of 11 bundles, showing the anterior limb of the internal capsule and cingulum as the most immature, followed by the optic radiations, arcuate and inferior longitudinal fascicles, then the spinothalamic tract and fornix, and finally the corticospinal tract as the most mature bundle. Thus, this approach provides new quantitative landmarks for further noninvasive research on brain-behavior relationships during normal and abnormal development.

DUBOIS J., DEHAENE-LAMBERTZ G., SOARES C., COINTEPAS Y., LE BIHAN D., HERTZ-PANNIER L.

Microstructural correlates of infant functional development: example of the visual pathways.

J. Neurosci., 28 (8), 1943-1948, 2008

(Services cités : Radiologie Pédiatrique, U663)

The development of cognitive functions during childhood relies on several neuroanatomical maturation processes. Among these processes is myelination of the white matter pathways, which speeds up electrical conduction. Quantitative indices of such structural processes can be obtained in vivo with diffusion tensor imaging (DTI), but their physiological significance remains uncertain. Here, we investigated the microstructural correlates of early functional development by combining DTI and visual event-related potentials (VEPs) in 15 one- to 4-month-old healthy infants. Interindividual variations of the apparent conduction speed, computed from the latency of the first positive VEP wave (P1), were significantly correlated with the infants' age and DTI indices measured in the optic radiations. This demonstrates that fractional anisotropy and transverse diffusivity are structural markers of functionally efficient myelination. Moreover, these indices computed along the optic radiations showed an early wave of maturation in the anterior region, with the posterior region catching up later in development, which suggests two asynchronous fronts of myelination in both the geniculocortical and corticogeniculate fibers. Thus, in addition to microstructural information, DTI provides noninvasive exquisite information on the functional development of the brain in human infants.

KASSAI B., CHIRON C., AUGIER S., CUCHERAT M., REY E., GUEYFFIER F., GUERRINI R., VINCENT J., DULAC O., PONS G.

Severe myoclonic epilepsy in infancy: A systematic review and a meta-analysis of individual patient data.

Epilepsia, 49 (2), 343-348, 2008

(Services cités : Neurologie, U663)

Severe myoclonic epilepsy in infancy (SMEI) is a rare, but severe disorder with seizures typically resistant to conventional antiepileptic drugs. The objective of the present study was to systematically review the literature on the available treatments for SMEI. Databases searched included Medline, Embase, and Cochrane. We used a fixed effect model to summarize the odds ratio of seizures rates and a logistic model to evaluate the influence of patient characteristics on

treatment effect. We found 23 uncontrolled studies and 2 randomized controlled trials (RCTs) that compared stiripentol with placebo. Overall, 64 children aged between 3 and 20 years were included in the two RCTs. The odds ratio of responding to stiripentol relative to placebo was 32 (CI: 6.2, 161) and stiripentol reduced seizure rate by 70% (93%; 47%). The multivariate analysis does not suggest any differences within subgroups of participants and cotherapy. Results of uncontrolled studies in children with SMEI are potentially biased and do not provide valid information on the benefits and harms of treatments. The two RCTs identified, however, were performed with the same objectives and design and showed that seizure frequency is greatly reduced by stiripentol in children with SMEI after 2 months of treatment.

LE SAUX T., CHHUN S., REY E., LAUNAY O., WEISS L., VIARD J.P., PONS G., JULLIEN V.

Quantification of seven nucleoside/nucleotide reverse transcriptase inhibitors in human plasma by high-performance liquid chromatography with tandem mass-spectrometry.

J. Chromatogr. B (Anal. Technol. Biomed. Life Sci.), 865 (1-2), 81-90, 2008

(Services cités : Infectiologie, U663)

A simple analytical method was developed in 100µL of plasma for the simultaneous assay of the 7 nucleoside/nucleotide reverse transcriptase inhibitors (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zidovudine) currently used for the treatment of HIV-infected patients. After adding the internal standard, 6-beta-hydroxy-theophylline, plasma samples were precipitated with 500µL acetonitrile and the supernatants were evaporated to dryness. The residues were reconstituted with 500µL of water and 10µL of the extracts were injected in the chromatographic system. The chromatographic separation was performed with a C-18 column and a gradient mobile phase consisting of a mixture of water and acetonitrile, both containing 0.05% formic acid. Analytes quantification was performed by electrospray ionisation triple quadrupole mass-spectrometry in the positive mode using selected reaction monitoring (SRM). Intra- and inter-assay precision and accuracy were lower than 20% for the limit of quantification, and 15% for higher concentrations. The method has been implemented to assess plasma concentrations of patients infected by HIV and was found suitable for therapeutic drug monitoring.

NABBOUT R., DESGUERRE I., SABBAGH S., DEPIENNE C., PLOUIN P., DULAC O., CHIRON C.

An unexpected EEG course in Dravet syndrome.

Epilepsy Res., 81 (1), 90-95, 2008

(Services cités : Explorations Fonctionnelles, Neurologie, U663)

A puzzling EEG pattern combining frontal slow bi-tri spikes followed or not by slow waves when awake and activated by sleep with 5-10s discharges of 8-9Hz spikes in a minority of adolescents with Dravet syndrome (DS) was recorded in the context of stable seizure and cognitive status, and unchanged antiepileptic medication. Tonic seizures were frequently reported in patients with this EEG pattern (3/5). This EEG pattern could suggest that of Lennox-Gastaut syndrome (LGS) but it exhibits clear differences and therefore should not be considered as a change into LGS but as a previously overlooked unusual pattern in the adolescent course of DS.

**POIRIER K., EISERMANN M., CAUBEL I., KAMINSKA A., PEUDONNIER S.,
BODDAERT N., SAILLOUR Y., DULAC O., SOUVILLE I., BELDJORD C.,
LASCELLES K., PLOUIN P., CHELLY J., BAHI-BUISSON N.**

Combination of infantile spasms, non-epileptic seizures and complex movement disorder: a new case of ARX-related epilepsy.

Epilepsy Res., 80 (2-3), 224-228, 2008

(Services cités : Explorations Fonctionnelles, Neurologie, Radiologie Pédiatrique, U663)

Mutations in the ARX gene are responsible for a wide variety of mental retardation conditions including X-linked infantile spasms (ISSX) and generalized dystonia. However, electroclinical descriptions in patients with ISSX carrying ARX mutations are scarce. Here, we report on the electroclinical features of a 4-year-old boy with an expansion of the trinucleotide repeat in the ARX gene. Epilepsy started at 2 months of age with subclinical spasms that consisted of episodes of eye rolling combined with atypical hypsarrhythmia. Later, the condition evolved into severe mental retardation with polymorphic ictal episodes that consisted of nocturnal brief axial contractions followed by dyskinetic movement of all four limbs and diurnal clusters of chaotic movements combined with myoclonic jerks. EEG recording of these episodes lead to the diagnosis of non-ictal dyskinetic movements. This combination of early infantile spasms followed by a complex movement disorder contributes further to extent the pleiotropy of the ARX-linked "interneuronopathy" and should lead the clinician to ARX mutation screening.

2007

AMIEL J., RIO M., PONTUAL L.D., REDON R., MALAN V., BODDAERT N., PLOUIN P., CARTER N.P., LYONNET S., MUNNICH A., COLLEAUX L.

Mutations in TCF4, Encoding a Class I Basic Helix-Loop-Helix Transcription Factor, Are Responsible for Pitt-Hopkins Syndrome, a Severe Epileptic Encephalopathy Associated with Autonomic Dysfunction.

Amer. J. Hum. Genet., 80 (5), 988-993, 2007 ; (Facteur d'Impact 2006 : **12,629**)

(Services cités : Génétique Médicale Pédiatrique, Radiologie Pédiatrique, U781, U663)

Pitt-Hopkins syndrome (PHS) is a rare syndromic encephalopathy characterized by daily bouts of hyperventilation and a facial gestalt. We report a 1.8-Mb de novo microdeletion on chromosome 18q21.1, identified by array-comparative genomic hybridization in one patient with PHS. We subsequently identified two de novo heterozygous missense mutations of a conserved amino acid in the basic region of the TCF4 gene in three additional subjects with PHS. These findings demonstrate that TCF4 anomalies are responsible for PHS and provide the first evidence of a human disorder related to class I basic helix-loop-helix transcription-factor defects (also known as "E proteins"). Moreover, our data may shed new light on the normal processes underlying autonomic nervous system development and maintenance of an appropriate ventilatory neuronal circuitry.

BAHI-BUISSON N., VILLANUEVA V., BULTEAU C., DELALANDE O., DULAC O., CHIRON C., NABOUT R.

Long term response to steroid therapy in Rasmussen encephalitis.

Seizure - Eur. J. Epilep., 16 (6), 485-492, 2007 ; (Facteur d'Impact 2006 : **1,384**)

(Services cités : Neurologie, U663)

Rasmussen encephalitis (RE) is a severe and progressive focal epilepsy of unknown origin that leads to deterioration of motor and cognitive function. In a previous study, we described positive effect of high doses of steroids during the first year after the onset of RE. The objective of this study was to evaluate this therapy at long term. We reviewed 11 patients (7 girls and 4 boys) with RE of the right hemisphere (7) and the left (4) at a follow-up of 9+/-2 years. Age at onset of RE ranged from 2 to 14 years. Six patients had no benefit from steroid therapy and underwent hemispherotomy. Five had significant reduction of seizure frequency with disappearance of epilepsia partialis continua, and improved motor function. Of these, two died of unexpected sudden death 5 and 7 years after seizure control. Two others with initial response experienced progressive recurrence of seizures 1 to 4 years after the end of steroid therapy and required hemispherotomy. Finally, only one patient exhibited total cessation of seizures with steroids for 3 years, but seizures progressively recurred although the frequency was moderate. Our data confirm that although steroid treatment can be useful when given early in the course of RE, long term relapse can occur among the good responders requiring delayed hemispheric disconnection.

CHIRON C.

Stiripentol.

Neurotherapy, 4 (1), 123-125, 2007 ; (Facteur d'Impact 2006 : **X**)

(Services cités : U663, Neurologie)

Stiripentol (STP) is a new antiepileptic compound made by Biocodex. It recently proved to increase the GABAergic transmission in vitro in an experimental model of immature rat. Clinical studies were based on the fact that STP also acts as an inhibitor of CYP3A4, CYP1A2, and CYP2C19 in vivo in epileptic patients. Whereas the studies in adult patients were disappointing, the trials conducted in pediatric populations demonstrated a specific efficacy of STP in severe myoclonic epilepsy in infancy, Dravet syndrome, when combined with valproate and clobazam. Based on these results, STP was granted orphan drug status in the European Union for the treatment of Dravet syndrome. The French experience in compassionate use suggests that STP might also be of benefit when combined with carbamazepine in pediatric patients with pharmaco-resistant partial epilepsy. The interactions of STP with a large number of drugs need to be carefully taken into account, with doses of the combined antiepileptic drugs adjusted to improve the tolerability of the therapeutic association.

CO J.P.T., ELIA M., ENGEL J.J.R., GUERRINI R., MIZRAHI E.M., MOSHE S.L., PLOUIN P.

Proposal of an algorithm for diagnosis and treatment of neonatal seizures in developing countries. *Epilepsia*, 48 (6), 1158-1164, 2007 ; (Facteur d'Impact 2006 : **3,526**)

(Services cités : Explorations Fonctionnelles, U663)

Seizures in the neonatal period are common. They can be caused by a variety of conditions, ranging from benign, self-limited illnesses to severe, life-threatening disorders. They are often the first sign of neurologic dysfunction in neonates, and may be used as one factor in considering long-term prognosis. An important mission of the International League Against Epilepsy (ILAE) is to improve the care of patients with epilepsy. Most recently, as part of the Global Campaign against Epilepsy, ILAE, in conjunction with the World Health Organization (WHO), established a new initiative to create clinical guidelines and diagnostic and management algorithms for the care of patients with seizures that can be applied worldwide, including in developing countries with limited or varied medical resources. Created by an international panel of experts in seizure management and guideline development, this document proposes guidelines for the diagnosis and management of the most common and important conditions that cause seizures in the neonatal period. The publication of these clinical pathways for neonatal seizures will be followed by a period of field testing and comment by WHO clinicians and officials before finalization.

DULAC O., JAMBAQUE I., CHIRON C.

'Severe memory impairment in a child with bihippocampal injury after status epilepticus' - The authors reply.

Dev. Med. Child Neurol., 49 (5), 399, 2007 ; (Facteur d'Impact 2006 : **2,008**)

(Services cités : Neurologie, U663)

DULAC O., NABBOUT R., PLOUIN P., CHIRON C., SCHEFFER I.E.

Early seizures: causal events or predisposition to adult epilepsy ?

Lancet Neurol., 6 (7), 643-651, 2007 ; (Facteur d'Impact 2006 : **9,479**)

(Services cités : Neurologie, U663, Explorations Fonctionnelles)

Past studies have been unable to confirm whether early seizures predispose to epilepsy in adults. Seizures in infancy were classically thought to cause brain lesions that led to epilepsy in adulthood. However, these infants were not thought to have epilepsy, but acute events that included seizures. Accumulating evidence suggests that early seizures may be associated with, or cause, brain damage; or alternatively, they may be the first expression of a genetic or lesional predisposition to epilepsy. The course of early seizures ranges from transient to life-long, depending on epilepsy syndrome, causes, and treatment. The main factors that determine late or persisting epilepsy after the occurrence of early seizures are protracted seizures, tonic seizures, and involvement of mesial temporal structures. A developmental approach to seizure disorders will aid understanding of epilepsy in adults and improve the design of antiepileptic agents for children and adults.

HIRT D., URIEN S., JULLIEN V., FIRTION G., CHAPPUY H., REY E., PONS G., MANDELBROT L., TRELUYER J.M.

Pharmacokinetic modelling of the placental transfer of nelfinavir and its M8 metabolite: a population study using 75 maternal-cord plasma samples.

Br. J. Clin. Pharmacol., 64 (5), 634-644, 2007 ; (Facteur d'Impact 2006 : **2,718**)

(Services cités : CUDR, U663)

AIMS: A population pharmacokinetic model was developed to characterize the transfer of nelfinavir and its active metabolite M8 from maternal to cord plasma and amniotic fluid.

METHODS: Concentration data were obtained from 75 women on the day of delivery and for whom maternal, umbilical plasma and amniotic fluid samples were collected. Data from 53 pregnant, 61 nonpregnant and seven consecutively pregnant and non pregnant women were then added to the database, the contents of which were analyzed using NONMEM. **RESULTS:**

Nelfinavir and M8 concentrations in maternal plasma, umbilical plasma and amniotic fluid were described by six connected compartments. Mean (% intersubject variability) population estimates were: absorption rate 0.67 h⁻¹, lag time 0.87 h, oral clearance and volume of distribution: 39.5 l h⁻¹ (53%), and 557 l for non pregnant and pregnant women, respectively, and 115 l h⁻¹ (132%) and 1626 l, respectively, on the day of delivery, M8 formation clearance 0.77 l h⁻¹ and M8 elimination rate constant 0.34 h⁻¹ (74%). For nelfinavir and M8, respectively, the mother-to-cord parameters were 0.058 l h⁻¹ (34%), and 0.35 h⁻¹ (76%), the cord-to-amniotic fluid rate constants were 0.23 and 0.59 h⁻¹, and the elimination rate constants from amniotic fluid were 0.36 and 0.49 h⁻¹. The nelfinavir fetus : maternal concentration ratio was 25% for maternal concentrations between 0.1 and 2.5 mg l⁻¹, between the 31 and 41st week of gestation.

CONCLUSIONS: The low transfer of nelfinavir from the placenta is unlikely to protect the fetus from vertical HIV-1 transmission.

JAMBAQUE I., DELLATOLAS G., FOHLEN M., BULTEAU C., WATIER L., DORFMULLER G., CHIRON C., DELALANDE O.

Memory functions following surgery for temporal lobe epilepsy in children.

Neuropsychologia, 45 (12), 2850-2862, 2007 ; (Facteur d'Impact 2006 : **3,924**)

(Services cités : Neurologie, U663)

Surgical treatment appears to improve the cognitive prognosis in children undergoing surgery for temporal lobe epilepsy (TLE). The beneficial effects of surgery on memory functions,

particularly on material-specific memory, are more difficult to assess because of potentially interacting factors such as age range, intellectual level, left-handedness, type of surgery and seizure outcome. This study investigated memory functions in 20 right-handed children who had left or right-temporal lobe surgery - including hippocampectomy - and became seizure-free. The neuropsychological evaluation included tests measuring verbally and visually mediated episodic memory, everyday memory as well as attention/working memory and language/semantic memory. We also assessed the relationships between age of seizure onset, general cognitive ability and memory functions. Children with TLE showed poor memory efficiency before surgery that tended to improve about 1 year after surgery. We found a material-specific memory effect, especially after surgery-9 (out of 12) children with left TLE had worse verbal memory results while 5 (out of 8) with right TLE had worse visual memory results. Post-operatively, most children had poor everyday memory performance on the Rivermead Behavioural Memory Test. No significant relationship was observed between episodic memory scores and age of epilepsy onset but children with early onset remained with lower Performance IQ values, Rey's figure copy scores and naming performances after surgery. Surgery significantly improved all the attention/working memory scores, some verbal episodic memory tasks and naming test performances. A different pattern of episodic and semantic memory limitations related to left or right TLE was observed.

KAMINSKA A., MOURDIE J., BARNERIAS C., BAHU-BUISSON N., PLOUIN P., HUON C.

Management of neonatal seizures.

Archives Pédiatrie, 14 (9), 1137-1151, 2007 ; (Facteur d'Impact 2006 : **0,258**)

(Services cités : Explorations Fonctionnelles, U663, Neurologie)

The aim of this review is to focus on the nosological classification of neonatal << convulsions >>, to precise the underlying aetiologies and the prognosis, and to propose diagnostic and therapeutical approach. Seizures may be epileptic or not, they may be occasional, part of an epilepsy syndrome or associated to a metabolic disease. Electroencephalography plays a central role; it enables to confirm the epileptic nature of the ictal events, it allows to evaluate the prognosis and to guide the treatment decision, and sometimes may help in the etiological diagnosis. Work up should include cerebral imaging (MRI) completed by other exams according to the diagnostic hypothesis. It is essential to go as far as possible in the etiological work-up not to attribute convulsions to an occasional event as HIE in which criteria remain very strict, when convulsions could be due to genetic origin or to maternal pathology. Treatment decision should comprise different ways: treatment of the underlying cause, of the eventual associated pathologies, maintenance of vital functions and antiepileptic treatment. Phenobarbitone remains the first line drug in occasional seizures, and second line drugs for which further studies are needed both for immediate and long-term secondary effects. Besides occasional seizures epilepsy syndromes and metabolic diseases remain exceptional. Nevertheless recognition of these conditions allows to establish the prognosis and to start immediately with an appropriate and specific medication depending on the epilepsy syndrome and can contribute to a prenatal diagnosis. It is important to recognize the inborn errors of metabolism because emergency appropriate treatment is required. Prognosis which is generally bad is essentially related to the underlying aetiology and probably to the duration of the active period of seizures.

NABBOU R., BAULAC S., DESGUERRE I., BAHI-BUISSON N., CHIRON C., RUBERG M., DULAC O., LEGUERN E.

New locus for febrile seizures with absence epilepsy on 3p and a possible modifier gene on 18p. *Neurology*, 68 (17), 1374-1381, 2007 ; (Facteur d'Impact 2006 : **5,690**)
(Services cités : Neurologie, U663)

OBJECTIVE: To report a clinical and genetic study of a large family with febrile seizures (FS) and childhood absence epilepsy (CAE). **METHODS:** This family was identified through a French campaign for familial epilepsies. It spans four generations and consists of 51 members, 13 of whom were affected. The medical history of all members was obtained by personal information and by consulting the medical files of affected members. All family members gave written consent to participate in the study. **RESULTS:** All affected members presented FS, with CAE in five and temporal lobe epilepsy (TLE) in one. FS stopped before age 6 years in all but one patient. FS were simple, except in one patient who had a long-lasting complex FS at 8 months of age. He later presented pharmaco-resistant TLE and left hippocampal sclerosis was visible on brain MRI. Patients presenting CAE had recorded absences and characteristic EEGs with 3 Hz spike waves. After exclusion of reported loci for FS and generalized epilepsy with FS plus, a genome-wide search allowed us to map a new locus for FS on 3p. We could not exclude another genomic segment on chromosome 18p and all patients presenting epilepsy (CAE and TLE) shared a common haplotype at this locus in addition to the haplotype on 3p. **CONCLUSION:** These findings emphasize the genetic heterogeneity of febrile seizures. Furthermore, epilepsy in association with febrile seizures might result in this family from an interaction between at least two genes: the gene on 3p and a possible modifier gene on 18p.

NGOUNGOU E.B., POUDIOUGOU B., DULAC O., DICKO A., BONCOEUR M.P., TRAORE A.M., COULIBALY D., KEITA M.M., PREUX P.M., DOUMBO O.K., DRUET-CABANAC M.

Persistent neurological sequelae due to cerebral malaria in a cohort of children from Mali. *Rev. Neurol.*, 163 (5), 583-588, 2007 ; (Facteur d'Impact 2006 : **0,501**)
(Services cités : Neurologie, U663)

INTRODUCTION: Several neurological complications are associated with cerebral malaria (CM). However, few long-term data from childhood survivors have been published. **METHODS:** A cross-sectional study was carried out in Mali among children followed from 1999 to 2002 after serious and complicated malaria. Our aim was to evaluate the persistent neurological sequelae associated with CM. **RESULTS:** This study concerned 101 subjects who had had CM. Mean age was 5.6+/-3.6 years. Twenty-eight children presented persistent neurological sequelae (27.7p.cent). Among them eight (7.9p.cent) children had developed these sequelae just after CM and 20 (19.8p.cent) a few months later: headaches, mental retardation, speech delay, bucco-facial dyspraxia, diplegia and frontal syndrome (one case each), dystonia (two cases), epilepsy (five cases) and behavior and attention disorders (15 cases). **CONCLUSIONS:** In this study, we show that neurological signs due to CM can persist in the long run. Long-term follow-up and proper management after CM are essential.

PIERIBONE V.A., TSAI J., SOUFFLET C., REY E., SHAW K., GILLER E., DULAC O.

Clinical evaluation of ganaxolone in pediatric and adolescent patients with refractory epilepsy. *Epilepsia*, 48 (10), 1870-1874, 2007 ; (Facteur d'Impact 2006 : **3,526**)

(Services cités : Neurologie, U663)

PURPOSE: A pilot study of the safety, tolerability, dose range and potential efficacy of ganaxolone for the treatment of refractory epilepsy in pediatric and adolescent subjects.

METHODS: We report the results of a nonrandomized, nonblinded, open-label, dose-escalation trial of ganaxolone in pediatric subjects (5-15 years) suffering from refractory epilepsy. Subjects received an oral suspension of ganaxolone in a 1:1 complex with beta-cyclodextrin in a dose escalation (1 mg/kg, b.i.d. to 12 mg/kg t.i.d.) schedule over 16 days. This was followed by a maintenance period for 8 weeks. Subjects that showed significant response were eligible for a compassionate use extension period. **RESULTS:** Fifteen subjects enrolled, eight completed the trial and three continued in the open-label compassionate-use extension period. All subjects exhibited refractory partial or generalized epilepsy. In an intent-to-treat analysis, four (25%) were considered substantial responders ($\geq 50\%$ reduction in seizure frequency), two (13%) were considered moderate responders (between 25 and 50% reduction in seizure frequency) and the remainder were considered nonresponders ($< 24\%$ reduction). Three subjects entered the extension phase, one remained essentially seizure-free for over 3.5 years of ganaxolone administration. Ganaxolone was tolerated well. A total of 17 adverse events were reported in 10 patients, all were considered mild to moderate in severity. Somnolence was the most frequently (nine) reported adverse event. **CONCLUSIONS:** This pilot study is consistent with other clinical studies indicating that ganaxolone has anticonvulsant activity in humans. The results of this study encourage the further study of ganaxolone as an antiepileptic therapy.

PINTAUDI M., EISERMANN M.M., VILLE D., PLOUIN P., DULAC O., KAMINSKA A.

Can fever treat epileptic encephalopathies ?

Epilepsy Res., 77 (1), 44-61, 2007 ; (Facteur d'Impact 2006 : **2,088**)

(Services cités : Neurologie, U663)

PURPOSE: To describe resistant epileptic encephalopathies that significantly improved after an acute febrile episode (FE). **METHODS:** We reviewed the clinical history of patients with daily pharmacoresistant seizures referred to the Saint-Vincent de Paul Hospital in the last 5 years. Four patients experienced seizure arrest in relation with a febrile episode. **RESULTS:** The four patients suffered from epileptic encephalopathy. Three were symptomatic, one cryptogenic. They presented spasms and atypical absences, beginning after the age of 1 year. All seizures stopped at the onset of fever, and significant EEG improvement was observed. The seizure-free period ranged from 2 to 24 months. **DISCUSSION AND CONCLUSION:** The close link between the occurrence of FE and the disappearance of seizures and EEG improvement, contrasting with the previous pharmacoresistance of this epileptic encephalopathy, supports a non fortuitous association. Several mechanisms could explain this phenomenon, including viral etiology, hyperthermia, inflammatory-immune reaction and ACTH release. Better understanding this phenomenon could open new therapeutic perspectives.

2006

BAHI-BUISSON N., MENTION K., LEGER P.L., VALAYANOPOULOS V., NABBOUT R., KAMINSKA A., PLOUIN P., DULAC O., de LONLAY P., DESGUERRE I.

Neonatal epilepsy and inborn errors of metabolism.

Archives Pédiatrie, 13 (3), 284-292, 2006

(Services cités : Explorations Fonctionnelles, Métabolisme-Neurologie, U663)

Metabolic disorders constitute an important cause of neurologic disease, including neonatal epilepsy. Epilepsy rarely dominates the clinical presentation, which is more frequently associated with other neurologic symptoms, such as hypotonia and/or vigilance disturbances. In most cases, epilepsy secondary to inherited metabolic disorders presents with polymorphic clinical and electrographic features that are difficult to classify into precise epileptic syndromes. However, specific types of seizures, such as myoclonic seizures or distinctive electroencephalographic patterns, such as suppression burst patterns, epileptic syndrome or early myoclonic encephalopathy, may suggest a specific metabolic disease. The aim of this article is to help clinicians in reviewing potential metabolic diagnoses and approaching metabolic evaluations.

BAHI-BUISSON N., SAVINI R., EISERMANN M., BULTEAU C., DULAC O., HERTZ-PANNIER L., CHIRON C.

Misleading effects of clonazepam in symptomatic electrical status epilepticus during sleep syndrome.

Pediat. Neurol., 34 (2), 146-150, 2006

(Services cités : Métabolisme-Neurologie, Radiologie Pédiatrique, U663)

Electrical status epilepticus during sleep syndrome and its variants are age-dependent epileptic encephalopathies associated with a sleep-related electroencephalographic pattern of continuous spike-waves, combined with motor or cognitive impairment. These epileptic encephalopathies are usually not responsive to conventional antiepileptic drugs. This report describes two children in whom clonazepam had no effect on cognitive and motor disorders but controlled spike activity, preventing a proper diagnosis. Withdrawal of clonazepam was accompanied by the recurrence of continuous spike-waves in slow sleep, permitting the diagnosis of electrical status epilepticus during sleep syndrome and appropriate therapeutic decisions. These two cases of the misleading effect of clonazepam in electrical status epilepticus during sleep syndrome illustrate the puzzling situation that can occur when therapeutic options only consider the electroencephalographic features without prior syndromic diagnosis.

BAHI-BUISSON N., CHELLY J., DES PORTES V.

Update on the genetics of X-linked mental retardation.

Rev. Neurol., 162 (10), 952-963, 2006

(Services cités : Métabolisme-Neurologie, U663)

Mutations in X-linked genes are likely to account for the observation that more males than females are affected with mental retardation. Causative mutations have been identified in both syndromic XLMR and in the genetically heterogeneous non-syndromic forms of XLMR, without a clear clinical phenotype other than cognitive deficit. Progress in genome analysis and the

establishment of large collaborations between clinical and molecular research teams, especially the European XLMR consortium, have led to the identification of 20 non-syndromic XLMR genes and 25 syndromic XLMR genes. Given the extensive heterogeneity of non syndromic XLMR, different strategies are used for the identification of new genes: linkage analysis, studies of balanced chromosomal rearrangements (X-autosome translocations, microdeletions) and candidate genes strategies by mutation screening in regions of the X chromosome known to be involved in neuronal development and function. Delineating the monogenic causes of XLMR and their molecular and cellular consequences will provide insight into the mechanisms that are required for normal development of cognitive function in humans. Non syndromic XLMR proteins include 5 distinct classes: transmembrane receptors, small GTPases effectors or regulators, enzymes and translational regulators.

CHIRON C., TONNELIER S., REY E., BRUNET M.L., TRAN A., D'ATHIS P., VINCENT J., DULAC O., PONS G.

Stiripentol in childhood partial epilepsy: Randomized placebo-controlled trial with enrichment and withdrawal design.

J. Child Neurol., 21 (6), 496-502, 2006

(Services cités : [Métabolisme-Neurologie, U663](#))

Stiripentol, a new antiepileptic drug inhibiting cytochrome P450-enzymes, suggested some efficacy when combined with carbamazepine in an open trial in refractory partial epilepsy of childhood. Our objective was to test these results in a placebo-controlled trial. To limit the number of patients included, we used an enrichment and withdrawal design. Among the 67 children entered in a 4-month open add-on stiripentol study following a 1-month single-blind placebo baseline, the 32 responders were randomized for 2 months either to continue stiripentol (n = 17) or to withdraw to placebo (n = 15). If seizures increased by at least 50% after randomization compared with baseline, the patients dropped out (primary end point): there were six patients on stiripentol and eight patients on placebo (not significant). However, a decrease in seizure frequency compared with baseline (secondary end point) was greater on stiripentol (-75%) than on placebo (-22%) (P <.025). Twelve patients experienced at least one adverse event on stiripentol (71%) compared with four patients on placebo (27%); none were reported as severe. The combination of stiripentol and carbamazepine proved to reduce seizure frequency in children with refractory partial epilepsy, although it failed to show a significant impact according to the escape criteria selected as the primary end point in the present study, for ethical reasons.

DEHAENE-LAMBERTZ G., HERTZ-PANNIER L., DUBOIS J., MERIAUX S., ROCHE A., SIGMAN M., DEHAENE S.

Functional organization of perisylvian activation during presentation of sentences in preverbal infants.

Proc. Nat. Acad. Sci. USA, 103 (38), 14240-14245, 2006

(Services cités : [Radiologie Pédiatrique, U663](#))

We examined the functional organization of cerebral activity in 3-month-old infants when they were listening to their mother language. Short sentences were presented in a slow event-related functional MRI paradigm. We then parsed the infant's network of perisylvian responsive regions into functionally distinct regions based on their speed of activation and sensitivity to sentence repetition. An adult-like structure of functional MRI response delays was observed along the superior temporal regions, suggesting a hierarchical processing scheme. The fastest responses were recorded in the vicinity of Heschl's gyrus, whereas responses became increasingly slower

toward the posterior part of the superior temporal gyrus and toward the temporal poles and inferior frontal regions (Broca's area). Activation in the latter region increased when the sentence was repeated after a 14-s delay, suggesting the early involvement of Broca's area in verbal memory. The fact that Broca's area is active in infants before the babbling stage implies that activity in this region is not the consequence of sophisticated motor learning but, on the contrary, that this region may drive, through interactions with the perceptual system, the learning of the complex motor sequences required for future speech production. Our results point to a complex, hierarchical organization of the human brain in the first months of life, which may play a crucial role in language acquisition in our species.

DEHAENE-LAMBERTZ G., HERTZ-PANNIER L., DUBOIS J.

Nature and nurture in language acquisition: anatomical and functional brain-imaging studies in infants.

Trends Neurosci., 29 (7), 367-373, 2006

(Services cités : Radiologie Pédiatrique, U663)

Speech processing in adults relies on precise and specialized networks, located primarily in the left hemisphere. Behavioral studies in infants indicate that a considerable amount of language learning already takes place in the first year of life in the domains of phonology, prosody and word segmentation. Thanks to neuroimaging, we can move beyond behavioral methods and examine how the infant brain processes verbal stimuli before learning. These studies reveal a structural and functional organization close to what is described in adults and suggest a strong bias for speech processing in these regions that might guide infants as they discover the properties of their native language, although no evidence can be provided as yet for speech specificity of such networks. This review is part of the INMED/TINS special issue "Nature and nurture in brain development and neurological disorders", based on presentations at the annual INMED/TINS symposium (<http://inmednet.com/>).

DUBOIS J., HERTZ-PANNIER L., DEHAENE-LAMBERTZ G., COINTEPAS Y., LE BIHAN D.

Assessment of the early organization and maturation of infants' cerebral white matter fiber bundles: a feasibility study using quantitative diffusion tensor imaging and tractography.

Neuroimage, 30 (4), 1121-1132, 2006

(Services cités : Radiologie Pédiatrique, U663)

The human infant is particularly immature at birth and brain maturation, with the myelination of white matter fibers, is protracted until adulthood. Diffusion tensor imaging offers the possibility to describe non invasively the fascicles spatial organization at an early stage and to follow the cerebral maturation with quantitative parameters that might be correlated with behavioral development. Here, we assessed the feasibility to study the organization and maturation of major white matter bundles in eighteen 1- to 4-month-old healthy infants, using a specific acquisition protocol customized to the immature brain (with 15 orientations of the diffusion gradients and a 700 s mm⁻²b factor). We were able to track most of the main fascicles described at later ages despite the low anisotropy of the infant white matter, using the FACT algorithm. This mapping allows us to propose a new method of quantification based on reconstructed tracts, split between specific regions, which should be more sensitive to specific changes in a bundle than the conventional approach, based on regions-of-interest. We observed variations in fractional anisotropy and mean diffusivity over the considered developmental period in most bundles (corpus callosum, cerebellar peduncles, cortico-spinal tract, spino-thalamic tract, capsules,

radiations, longitudinal and uncinate fascicles, cingulum). The results are in good agreement with the known stages of white matter maturation and myelination, and the proposed approach might provide important insights on brain development.

JAMBAQUE I., HERTZ-PANNIER L., MIKAELOFF Y., MARTINS S., PEUDENIER S., DULAC O., CHIRON C.

Severe memory impairment in a child with bihippocampal injury after status epilepticus.

Dev. Med. Child Neurol., 48 (3), 223-226, 2006

(Services cités : Radiologie Pédiatrique, U663, Métabolisme-Neurologie)

Epilepsy may contribute to memory deficits in children, but these deficits are generally mild. We describe the neuropsychological profile of a female who had prolonged status epilepticus at 5 years of age, and then developed temporal lobe epilepsy. Brain magnetic resonance imaging 1 month after the onset of status epilepticus showed marked bilateral hippocampal atrophy that seemed disproportionate to the mild cortico-subcortical atrophy. At the age of 7 years, this child had cognitive impairment (an IQ of 62), which particularly affected her memory. This included short-term memory, and immediate and delayed memory deficits for verbal and visual materials that had a profound impact on everyday life. This observation demonstrates that severe status epilepticus can cause predominant bilateral hippocampal atrophy in childhood. In contrast with children who develop such damage after anoxia, this may result in general cognitive impairment but also in more severe episodic memory deficit.

KROLL-SEGER J., PORTILLA P., DULAC O., CHIRON C.

Topiramate in the treatment of highly refractory patients with dravet syndrome.

Neuropediatrics, 37 (6), 325-329, 2006 ; (Facteur d'Impact 2005 : **1,619**)

(Services cités : Métabolisme-Neurologie, U663)

The purpose of this study was to assess the effectiveness and tolerability of topiramate (TPM) as add-on therapy in children with Dravet syndrome and considered unsatisfactorily controlled using stiripentol. All the 36 patients having been treated with TPM in our centre in 2001 were retrospectively evaluated. Seventy percent of them still received stiripentol when TPM was introduced. The association of both drugs did not need any particular adaptation of dosages. The mean TPM follow-up was 13.3 months (4 - 25 months) and the mean optimal TPM dose was 3.2 mg/kg/d (0.6 - 9.2 mg/kg/d). Twenty eight children (78 %) showed more than 50 % reduction in the frequency of generalized tonic-clonic seizures and status epilepticus (SE), whereas 8 % had more than 50 % increase. Six patients (17 %) remained seizure-free for at least 4 months. The most frequently reported side-effects were gastrointestinal and behavioural disturbances. TPM had to be stopped in 17 % of patients, because of poor tolerability and/or lack of efficacy. Topiramate seems therefore to be helpful in Dravet syndrome, even in patients not satisfactorily controlled by stiripentol. Both drugs can be easily and safely associated.

MARTINS S., GUILLERY-GIRARD B., JAMBAQUE I., DULAC O., EUSTACHE F.

How children suffering severe amnesic syndrome acquire new concepts ?

Neuropsychologia, 44 (14), 2792-2805., 2006

(Services cités : U663)

Recent studies revealed that children with developmental amnesia acquired new semantic information. However, they failed to investigate the growth of such knowledge during childhood, and they did not bring evidence concerning the putative role of residual episodic memory in semantic acquisition. This prospective study sought to clarify this issue by assessing both

semantic and episodic memory in two amnesic children (RH and KF) with different neuropsychological profiles. We thus applied errorless semantic learning and vanishing cues methods, together with assessments of episodic memory using original recognition tasks within the same protocol. Results demonstrated learning and long-lasting maintenance of multicomponent concepts (comprising labels, categories and features) in both amnesic children. Importantly, episodic memory assessments revealed differential residual abilities in these children, which may account for their respective profiles of semantic acquisition. Thus, RH, who demonstrated residual episodic abilities, acquired normally. However, the learning of KF, who had a massive impairment of episodic memory, remained slower than her controls. In conclusion, even though an episodic impairment may slacken new semantic learning, our research provides new evidence for the de novo acquisition of semantic concepts in childhood amnesic syndrome and strengthens the idea that semantic learning can occur without any recruitment of episodic memory.

MIKAELOFF Y., JAMBAQUE I., HERTZ-PANNIER L., ZAMFIRESCU A., ADAMSBAUM C., PLOUIN P., DULAC O., CHIRON C.

Devastating epileptic encephalopathy in school-aged children (DESC): a pseudo encephalitis.

Epilepsy Res., 69 (1), 67-79, 2006

(Services cités : Métabolisme-Neurologie, Radiologie Pédiatrique, U663)

PURPOSE: To describe the characteristics of a previously overlooked devastating epileptic encephalopathy that presents as intractable bilateral perisylvian epilepsy starting with prolonged status epilepticus (SE) in normally developing school-aged children. **METHODS:** Retrospective study over 7 years of all normally developing children admitted in our institution for a prolonged SE following non-specific febrile illness with at least one seizure recorded on EEG. **RESULTS:** Fourteen children were included at a median age of 7.5 years (4-11) (median follow-up of 4 years (1-7)). Intractable SE lasted 4-60 days (median 30). CSF cell count was normal in five cases and moderately increased in the others. During SE, seizures were recorded in 11 patients and involved temporal lobes in 7; the other 4 patients exhibited perisylvian clinical features with secondary generalization. Intractable epilepsy followed SE in all cases without any latent period. Persisting seizures were recorded in 10 patients and involved temporo-perisylvian regions in 8, frontal regions in 2; 3 others had perisylvian ictal semiology. Spiking was bilateral in 10 cases. MRI showed bilateral hippocampal hypersignal and/or atrophy in 10 cases (extended to the neocortex in 3). All children had major cognitive sequelae. When feasible (six patients), detailed neuropsychology suggested fronto-temporal impairment. **CONCLUSIONS:** Among so called grey matter encephalitis patients, we identified a recognizable pattern we propose to call Devastating Epileptic encephalopathy in School-age Children (DESC) that begins with prolonged SE triggered by fever of unknown cause, and persists as intractable perisylvian epilepsy with severe cognitive deterioration.

QUILICHINI P.P., CHIRON C., BEN-ARI Y., GOZLAN H.

Stiripentol, a putative antiepileptic drug, enhances the duration of opening of GABA(A)-receptor channels.

Epilepsia, 47 (4), 704-716, 2006

(Services cités : Métabolisme-Neurologie, U663)

Purpose: Stiripentol (STP) is currently an efficient drug for add-on therapy in infantile epilepsies because it improves the efficacy of antiepileptic drugs (AEDs) through its potent inhibition of liver cytochromes P450. In addition, STP directly reduces seizures in several animal models of

epilepsy, suggesting that it might also have anticonvulsive effects of its own. However, its underlying mechanisms of action are unknown. Methods: We examined the interactions of STP with gamma aminobutyric acid (GABA) transmission by using patch-clamp methods in CA3 pyramidal neurons in the neonatal rat. Results: STP markedly increased miniature inhibitory postsynaptic current (mIPSC) decay-time constant in a concentration-dependent manner. The prolongation of mIPSC duration does not result from an interaction with GABA transporters because it persisted in the presence of GAT-1 inhibitors (SKF-89976A and NO-711). An interaction with benzodiazepine or neurosteroid binding sites also was excluded because STP-mediated increase of decay time was still observed when these sites were initially saturated (by clobazam, zolpidem, or pregnanolone) or blocked (by flumazenil or dehydroepiandrosterone sulfate), respectively. In contrast, saturating barbiturate sites with pentobarbital clearly occluded this effect of STP, suggesting that STP and barbiturates interact at the same locus. This was directly confirmed by using outside-out patches, because STP increased the duration and not the frequency of opening of GABA(A) channels. Conclusions: At clinically relevant concentrations, STP enhances central GABA transmission through a barbiturate-like effect, suggesting that STP should possess an antiepileptic effect by itself.

VILLE D., KAMINSKA A., BAHI-BUISSON N., BIRABEN A., PLOUIN P., TELVI L., DULAC O., CHIRON C.

Early pattern of epilepsy in the ring chromosome 20 syndrome.

Epilepsia, 47 (3), 543-549, 2006

(Services cités : Métabolisme-Neurologie, U663)

Summary: Purpose: The characteristics of epilepsy in ring chromosome 20 have been reported in adolescents and adults. The mode of onset most often remains imprecise. To clarify this onset period, we studied the early-onset features in our personal series and in the reported pediatric cases. Methods: Our series comprises one child with an onset of epilepsy in the neonatal period and five others with an onset before age 8 years. The cases in the literature with an epilepsy onset before 8 years also were reviewed. Results: Seizures in the neonatal period were described as motor seizures. Our personal patient with a neonatal onset had severe psychomotor delay. In both infancy and early childhood, the EEG showed no interictal frontal localization of the anomalies, and no long-lasting seizure was recorded. Seizures with terror and hallucinations usually appeared from about age 4 years. It is not before the age of 8 years that the usual interictal EEG pattern appeared of rhythmic theta slow-waves activity with spikes predominating in frontal areas described in adolescence and adulthood. The interictal EEG showed 1- to 2-Hz delta slow waves and spike-and-waves predominating in frontal areas, but no physiologic activity. Conclusions: In ring 20 chromosome, specific epilepsy features are lacking in the neonate, but the whole phenotype shows a more severe expression in terms of mental delay. The characteristic frontal EEG pattern and ictal terror do not appear before age 4 to 5 years.

2005

MOTTE J., PEDESPAN J.M., SEVESTRE M., CHIRON C.

Acceptability and tolerance of sodium valproate, a new sustained-action granule formulation, in monotherapy for epileptic children from 3 years old.

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Sodium valproate (VPA) is an anti-epileptic drug which was until now administered to children as drinkable or injectable form. A new galenic form of this compound has been developed as

microgranules with prolonged release (Micropakine)LP; MPK). This new galenic form of VPA allows a greater stability of the plasmatic rates, thus limiting the risk of amount-dependent adverse effects at the time of the peaks, and of less effectiveness at the time of the fall of the circulating rates. The main objective of this study was to evaluate the acceptability of the new galenic form of VPA, in monotherapy, for epileptic children with ≥ 3 years old. The evaluation was performed at day (D)90 by the patients using a hedonic visual scale. The secondary objectives were to evaluate the acceptability by the parents, the treatment compliance, the percentage of patients free of seizure at D 90, and the tolerance. Finally, the authors compared all these data to those recovered at the baseline in patients already treated by the previous drinkable VPA. A total of 307 patients were involved by 76 hospital neuropediatric physicians. The population was constituted by 110 children < 5 years old and 197 children from 5 to 14 years old. MPK was well accepted for total population at D 90 (< 5 years old: 83.3%; ≥ 5 years old: 80%). For patients previously treated by drinkable form of VPA (N=199), MPK was significantly better accepted than the drinkable form at D1 (< 5 years, $P=0.0189$; ≥ 5 years, $P<0.0001$). Less difficulties were experienced by the parents to administrate MPK when compared to the drinkable form ($P<0.001$), mainly due to his neutral taste. Patients free of seizure at D 90 were 77% [70,3; 82,5]. Specially, fewer epileptic seizures were evidenced for all children previously treated at D1 by drinkable form of VPA. The treatment was well respected by the patients, which were compliant in 80% of the cases. The adherence to treatment was good since the treatment compliance was 87%. MPK was well tolerated. CONCLUSION: MPK in the microgranule form significantly improves the treatment acceptability with a good tolerance. Two daily intakes and neutral taste are two major advantages to favour the compliance in children, thus contributing to the efficacy of the antiepileptic treatment.