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ABSTRACTS CLINIQUES

Children's at Home: Dedicated social media for parents of adolescents with Neurofibromatosis Type 1

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Purpose - To evaluate Children1s at Home(C@H), a social media website for parents of adolescents with Neurofibromatosis Typel(NFl).

Methods - Interventional study for parents of 13"18 year-olds with NFl including 2 phases: (1) Creating Video Intervention/Prevention Assessment (VIA) visual narratives about parenting a child with NFl; (2) Interacting on C@H, a secure, medically-moderated social media website using video and text. C@H was evaluated qualitatively via semi-structured phone interviews at enrollment(TO), after phase l(Tl), and after phase 2(T2).

Results - Seventeen mothers enrolled. At **TO,** participants reported not knowing anyone else with NFl and needing C@H to: break their isolation, connect with other families, and receive accurate information and support from others facing similar challenges. At **Tl,** participants reported improved awareness and quality of life and C@H created a forum to express their feelings and fears of having a child with NFl. At **T2,** participants reported: connecting with parents of children with NFl for the first time, valuing the "real *faces}}* and emotions of those with shared experiences. Creating an online comrnunity removed feelings of isolation and provided a sense of normalcy. Participants reported
feeling understood, relieved to talk about NFl, putting their lives into perspective, and finally addressing non-medical issues of NFl never discussed with doctors. Parents liked best about C@H: ending isolation, being part of a support group, accessing knowledge, and confidence in medical oversight. What parents liked least: technological issues and being reminded about the disease. The majority considered C@H a valuable 24/7 resource for living with NFl that should continue.

Conclusions - Many parents of adolescents with NFl feel isolated in their experience. C@H allowed them to connect for the first time. Innovative applications of social media dedicated to caregivers can provide peer-to-peer support and reliable medical information. Future research should test C@H using a non-categorical approach to chronic illness.

Evaluation et comparaison de la valeur prédictive de l'échelle « Braden Q » et de la « *Neonatal Skin Risk Assessment Scale* (NSRAS) » dans l'évaluation du risque d'escarre chez le nouveau-né hospitalisé

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Contexte
Les nouveau-nés sont à risque de développer des escarres dont la prévalence est un indicateur de qualité en raison du sur-risque de morbi-mortalité associé. Actuellement, il n'existe pas d'outil validé en langue française pour mesurer le risque d'escarre en néonatologie.

Objectifs
Traduire, tester et comparer la valeur prédictive positive (VPP) de deux échelles d'évaluation du risque d'escarre chez le nouveau-né.

Méthodes
Traduction des échelles de Braden Q et NSRAS selon la méthode de Wild, suivie d'une étude observationnelle prospective approuvée par la CER. Elle inclut des nouveau-nés hospitalisés en Néonatologie au CHUV entre octobre 2015 et janvier 2016.
Les patients inclus sont observés dès les premières 48h et jusqu'à 10 jours. L'évaluation du risque d'escarre s'effectue quotidiennement par deux cliniciens utilisant chacun une échelle de manière indépendante. Parallèlement et en insu de la cotation de l'échelle, l'infirmier en charge du patient évalue la présence d'escarres avec le Skin Assessment Tool (SAT) ; les escarres sont classifiées selon les grades de la NPUAP et photographiées. L'observation s'arrête en cas de survenue d'une escarre ou de sortie du service.

La sensibilité, la spécificité et la VPP de l'apparition d'escarre dans les 24 heures qui suivent chaque observation seront calculées et comparées entre les deux échelles à l'aide de tests Mc Nemar. Leur concordance sera estimée en utilisant la méthode Bland et Altman après standardisation des scores des deux échelles.

Résultats
Actuellement 51 des 80 patients ciblés ont été inclus, dont 6 (11.7%) ont développé une escarre. Les premiers résultats sont attendus pour janvier 2016.

Conclusion
Le déploiement d'échelles du risque d'escarre en néonatologie devrait contribuer au développement de stratégies et de recommandations visant à réduire l'incidence d'escarres chez les nouveau-nés hospitalisés, et participe ainsi à l'amélioration de la qualité et la sécurité des soins.

Gambling and risk behaviors: characteristics of young problematic gamblers in Switzerland

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Objective. To assess the characteristics and associated risk factors of young problematic gamblers.

Methods. Data were drawn from the GenerationFRee study, a Swiss cross-sectional in-school survey including 5179 youths aged 15-24(mean age 18.3). Among these participants, 1371 (26.5%) reported having gambled in the last 12 months and were included in the study. Gamblers were divided into two groups according to the South Oaks Gambling Screen(SOGS) scale: non-problematic gamblers(SOGS<2; N=1116) and at-risk/problematic gamblers(SOGS>=2; N=255). Participants reported demographic, family and academic data, risk behaviors(current smoking, alcohol misuse, cannabis and other illegal drugs use, violent and antisocial acts, and Internet addiction) and sensation seeking.

Results. At the bivariate level, at-risk/problematic gambling was positively associated with risk behaviors and sensation seeking. At-risk/problematic gamblers were significantly more likely to be male, older, non-Swiss born, apprentice, to live in an urban area, to have a non-intact family, foreign parents and to evaluate their socio-economic status as below average. Regarding the habits of participants' entourage, father, siblings and friends' gambling was positively associated with at-risk/problematic gambling. At the multivariate level, compared to non-problematic gamblers, at-risk/problematic gamblers were more likely to be males (aOR: 2.67 [1.75-4.09]), older (aOR: 1.14 [1.03-1.26]), to have friends who gambled (aOR: 3.73 [2.46-5.65]) and to be considered as a problematic Internet user (aOR: 2.56 [1.52-4.31]).

Conclusion. Gambling has become a very popular entertainment among adolescents and young adults. This activity may be considered harmless but it may increase the risk for addiction and social costs. Our results confirm the social aspect of this activity. Indeed, the strongest associated variable concerns friends' gambling. Although six of the seven studied risk behaviors disappeared in the multivariate analysis, the strong associations raised at the bivariate level demonstrate that gambling is part of a cluster of risk behaviors and thus represents also a concern among young people.

L'asphyxie néonatale : Un traumatisme ?

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Introduction: L'asphyxie néonatale concerne 2 enfants sur 1000, et entraine une mortalité et une morbidité importantes. De nombreuses publications décrivent la détresse et le stress post traumatique (PTSD) des parents d'enfants prématurés, aucune chez les parents d'enfants hospitalisés pour asphyxie néonatale.

Objectif : Comparer la santé mentale des parents d'enfants survivants traités par hypothermie pour une asphyxie néonatale, à celle d'un groupe contrôle.

Méthode : Etude cas-contrôle transversale des enfants enregistrés en 2012 et 2013 dans le registre suisse de l'asphyxie néonatale et ayant survécu. Des questionnaires de santé mentale (dépression, PTSD, attachement) ont été adressés aux parents et à une population contrôle contemporaine.

Résultats : Les questionnaires ont été remplis par les parents de 53/120 patients (51 mères et 44 pères du groupe asphyxie (MA et PA), et 137 mères et 57 pères du groupe contrôle (MC et PC) ; l'âge moyen était de 32 ans sans différence entre les groupes, 95% étaient en couple. Le score total de PTSD des MA et des PA était significativement plus élevé que les MC, avec significativement plus de symptômes d'intrusion, mais pas d'évitement. Les PA avaient significativement plus de symptômes d'hypervigilance que les PC. Parmi les MA, 30 % remplissaient les critères DSM-IV du PTSD, pour 16.8 % des MC ($p< 0.05$), et 10 (25.0%) des PA pour 6 (10.5%) % des PC ($p=0.054$). Il n'y avait pas de différence pour la dépression, par contre les mères d'enfants contrôle étaient significativement plus anxieuses. Pour finir, les scores d'attachement des MA étaient moins bons que ceux des MC.

Conclusion : Après asphyxie néonatale, les parents ont des problèmes de santé mentale avec des symptômes de stress post traumatique et d'anxiété importants. Il convient de reconnaître ces problèmes pour prévenir les troubles relationnels, et les troubles du développement chez l'enfant.

Les troubles du tonus transitoires chez des grands prématurés comme indicateurs cliniques précoces: corrélation avec l'IRM à terme et le suivi neuro-développemental à 18 mois.

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Introduction :
Un grand prématuré sur trois présentera des troubles cognitifs à l'âge scolaire pour lesquels il existe peu d'indicateurs cliniques précoces.
Les troubles transitoires du tonus (TTT) sont fréquents dans cette population avec des anomalies de posture, une hyperréflexie ou une motricité saccadée. Ils disparaissent avant l'âge de 2 ans et leur association avec le développement à long terme est peu décrite.
Objectifs :
Définir la prévalence du TTT dans une population de grands prématurés. Corrélation avec l'IRM à terme et le neurodéveloppement à 18 mois corrigés.
Méthodologie :
Etude prospective bicentrique (2007-2010) incluant des prématurés de <29 SA, sans lésions cérébrales majeures ou malformations, catégorisés en TTT+ ou TTT-. Evaluation par une IRM à terme (3T Verio Siemens) avec des séquences conventionnelles (pondérées T1 et T2) et diffusion (DTI), et un examen neurodéveloppemental (Bayley II) à 18 mois corrigés.
Résultats :
Nous avons inclu 108 patients, dont 34 (31%) TTT+ et 74 (69%) TTT-. Hormis pour la bronchodysplasie pulmonaire, les populations étaient comparables. A l'IRM, les coefficients de diffusion (ADC) et les valeurs d'anisotropie (FA) dans la substance blanche frontale, occipitale et le bras postérieur de la capsule interne (PLIC) sont significativement différents : ADC augmentés et FA abaissés chez les TTT+ (p= <0.05). Les indices de développement à 18 mois sont significativement diminués pour les TTT+ : MDI (mental) moyen de 80.42 (DS 19.13) vers 90.11 (DS 19.46, p=<0.05) pour les TTT- et PDI (moteur) moyen de 85.91 (DS 16.88) versus 92.15 (DS 20.39, p=<0.05).
Conclusion :
Les enfants TTT+ présentent plus de complications postnatales. De plus, l'étude confirme une association entre les TTT avec une substanche blanche plus immature à l'IRM à terme ainsi qu'un indice neurodéveloppemental diminué à 18 mois. Les TTT pourraient être un indicateur précoce de troubles du développement chez l'ancien prématuré.

A WxW motif bearing peptide can activate a distinct cell death program from known forms of death.

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BACKGROUND

Current oncological therapeutics aim to activate apoptosis to achieve disease control. Cancer cells however have developed resistance mechanisms to avoid death by either inactivating the pro-apoptotic machinery or by stimulating anti-apoptotic signaling. Strategies to eradicate neoplastic cells in an apoptosis-independent fashion would efficiently complement the existing anti-cancer strategies. The aim of the present study was to characterize the mode of death that is triggered by a WxW motif bearing peptide, called TAT-RasGAP$_{317-326}$. This cell permeable peptide derived from the p120 RasGAP protein was shown to bear anti-malignant properties in pediatric and adult tumors, such as inhibition of metastatic progression and tumor cell sensitization to cell death induced by anti-cancer therapies. We have previously shown that its anti-cancer activities are dependent on two tryptophan residues.

METHODS

TAT-RasGAP$_{317-326}$-induced cell death was assessed in two childhood cancer cell lines (Raji Burkitt lymphoma and NB1 neuroblastoma) using flow cytometry methods. To characterize the mode of death triggered by the peptide, we employed molecular biology assays and the CRISPR/Cas9 technology to generate specific gene knockouts.

RESULTS

Our results show that necroptosis, autophagy, parthanatos and pyroptosis are neither activated nor involved in the toxicity induced by TAT-RasGAP$_{317-326}$. In contrast, blocking apoptosis, either pharmacologically or genetically, did not (Raji cells), or only partially (NB1 cells), prevent TAT-RasGAP$_{317-326}$ cytotoxicity. Hence, TAT-RasGAP$_{317-326}$ induces both apoptosis and a novel described mode of non-canonical cell death. However, the latter remains to be better characterized.

CONCLUSION

As some pediatric cancer cells are particularly sensitive to this potentially novel mode of cell death, the WxW-bearing peptide is promising as a novel therapeutical approach, alone or in combination with existing drugs. However, its efficiency *in vivo* still needs to be assessed in this setting.

Genome-wide CRISPR/Cas9 screen to identify regulators of an uncharacterized form of cell death triggered by TAT-RasGAP$_{317-326}$.

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BACKGROUND

TAT-RasGAP$_{317-326}$ is a cell-permeable peptide derived from the p120 Ras GTPase-activating protein (RasGAP). It potently sensitizes childhood and adulthood tumor cells to various chemotherapeutic agents and hampers metastatic progression. Recently, we discovered that the RasGAP-peptide also possesses the ability to directly cause cell death in specific neoplastic cells populations (e.g. the Raji Burkitt lymphoma and the SKW6.4 B-lymphoblastoid EBV-transformed cells). Interestingly, blocking known modes of death (apoptosis, necroptosis, autophagy, parthanatos or pyroptosis) in these cells does not inhibit the toxicity of TAT-RasGAP$_{317-326}$. Therefore, our hypothesis is that using a Genome-scale CRISPR/Cas9 knockout screen, will allow us to identify regulators of a potentially novel modality of cell death mediated by TAT-RasGAP$_{317-326}$.

METHODS

We employed a CRISPR/Cas9 lentiviral library that can disrupt more than 19.000 genes to screen for regulators required for the toxicity of TAT-RasGAP$_{317-326}$ in Raji and SKW6.4 cells. Identification of candidate genes was performed by next-generation massively parallel genome sequencing with a MiSeq (Illumina). Validation was done by classic molecular biology assays and flow cytometry methods.

RESULTS

Our results revealed several attractive genetic modulators of the novel TAT-RasGAP$_{317-326}$-induced cell death. Top candidate genes share a potential common role in the killing efficacy of the peptide toward malignant cells. However, they can be involved at three different cellular steps: a) entry of the peptide into the cell, b) its endosomal escape and/or c) its pro-death activity once released from the endosomes. According to our results, the top candidates of the screening are involved at the endosomal escape of the peptide.

CONCLUSION

Our results while exciting are preliminary and further work is needed to validate the remaining candidates highlighted by the screen and confirm the molecular mechanisms involved. The ultimate aim is to identify genes that are required for the pro-death property of the peptide. This would permit to characterize which are the tumors that will respond to TAT-RasGAP$_{317-326}$-induced cell death.

RATTRAPAGE VACCINAL CHEZ LES ENFANTS MIGRANTS : EVALUATION DE L'INDICATION AUX SEROLOGIES VACCINALES

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INTRODUCTION
La couverture vaccinale de base s'est fortement répandue à travers le monde, rendant obsolète les schémas de revaccination complète chez les enfants migrants.

METHODE
Les patients migrants âgés de 12 mois à 18 ans, pris en charge à l'HEL, et ne pouvant pas fournir des détails sur les antécédents vaccinaux, ont été vaccinés avec un vaccin DTPa-IPV ± Hib et un vaccin contre l'hépatite B, suivis d'une sérologie tétanos et hépatite B, un mois plus tard. Un questionnaire a été complété afin d'identifier de possibles déterminants de la protection vaccinale.

RESULTATS (intermédiaires)
De septembre 2014 à octobre 2015, nous avons inclus 49 patients. Quarante-huit (98%) ont eu un bilan sérologique post-vaccinal. Quarant-sept (98%) avaient des taux d'anticorps antitétaniques conférant une protection à long terme. Un taux d'anticorps compatible avec une protection à long terme contre l'hépatite B a été retrouvé chez 29/48 patients (60.4%). Une hépatite B chronique a pu être exclue chez tous les enfants non-répondeurs. L'âge moyen des patients avec une protection à long terme contre l'hépatite B était significativement plus bas (8.7 vs 11.5 ans). On retrouvait aussi plus fréquemment, dans ce groupe de patients, une anamnèse positive pour un suivi dans un centre de santé (75% vs 38%, $p<0.05$) et le souvenir d'avoir été vacciné au moins une fois (96.4% vs 68.7%, $p<0.05$).

CONCLUSIONS
La couverture vaccinale de base est très élevée chez nos patients migrants. La preuve sérologique de la protection vaccinale antitétanique pourrait être abandonnée en l'absence d'éléments anamnestiques faisant évoquer une absence totale de vaccination antérieure. Un âge plus bas chez les enfants protégés à long terme contre l'hépatite B corrèle bien avec une augmentation récente de la couverture vaccinale. Cependant, aucun déterminant ne permet de prédire à 100% la protection vaccinale. Un contrôle sérologique reste donc pleinement indiqué.

Risk factors for severe RSV disease among immunocompromised patients

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Background: Respiratory syncytial virus (RSV) accounts for 90% of lower respiratory tract infections (LRTI) in children under 5 years of age. In hematopoietic stem cell transplant recipients (HSCT), mortality rates can reach up to 80%. Data on the burden and risk factors associated with severe RSV disease among immunocompromised patients are limited.

Objectives: 1) To determine the number of severe RSV-related respiratory illnesses among children and adults with an underlying immunosuppression. 2) To identify clinical and demographic risk factors for severe RSV disease.

Methods: Retrospective cohort study of RSV-related respiratory conditions documented among immunocompromised adults and children at the University hospitals of Lausanne and Geneva, Switzerland over a period of 10 years. Severe RSV-attributed respiratory condition was defined as LRTI or death with documentation of RSV from a respiratory sample. Information on socio-demographic and microbiololgical factors was collected through chart review. The potential association between predictors and severe RSV-attributed respiratory disease was assessed using multivariable logistic regression.

Preliminary results: 245 RSV-positive immunocompromised patients (180 adults (73.6%) and 65 (26.1%) children). Among these, 67 with HSCT (27.3%) and 65 solid-organ transplants (26.5%). Overall, almost half (46.9%) presented with LRTI, which resulted in a 37.6% admission rate, 13.5% admission rate to the intensive care unit (ICU) and a mortality rate of 10.6%, the latter exclusively adults. Thirty-three (15.1%) subjects required ribavirin, whereas 10 (4%) subjects (mainly adults) received palivizumab therapeutically. Multivariable analyses are currently ongoing.

Conclusions: RSV-related infections in immunocompromised adults result in higher rates of progression to LRTI compared to children. Underlying conditions such as higher rates of HSCT among adults may explain this difference. In this regard, multivariables analyses should better delineate other independent risk factors such as absolute lymphocyte (ALC) associated with progression to LRTI. This information may further stratify the need for preventive strategies such as palivizumab.

Assessment of mental suffering in male adolescents in Emergency: a nursing feasibility study

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Background: The adolescent mental health is a major concern. "Half of all mental health disorders in adulthood appears at age 14, but most cases are undetected and untreated (WHO, 2014) The first cause of the mental disease in adolescence is the depression. In Switzerland, the prevalence of the mental diseases in hospitalized adolescents aged from 10 to 14 years is 8.4% and of hospitalized male adolescents aged from 15 to 19 years is 13%.Globally, around 1.3 millions adolescents die each year. After road injury and HIV, the suicide is the third cause of death. In Switzerland, suicide remains the leading cause of death among young people aged 15-24 years. The male adolescents are concerned in majority. Rates of adolescent suicide attempts are underestimated and only 10-20% of them receive an appropriate care. Nowadays, when the male adolescents consult Paediatrics Emergency Departments (PED) for somatic reasons, an estimation and a treatment of physical pain stay the priority and the mental suffering often is directed only by intuition.
The screening for psychological distress with somatic manifestations in adolescence remains the best prevention.

Objectives : The goal of this research is to develop a nursing intervention in PED for the early detection of the mental suffering among male adolescent with somatic complaints.
Study aims :
1) Describe the components and characteristics of mental suffering of male adolescents.
2) Develop a systematic screening intervention of mental suffering in male adolescents and a nurse consultation in adolescent health.
3) Evaluate the feasibility of the intervention.

Methods : This feasibility study will be organized with a sequential exploratory mixed design.

Conclusions : This research will contribute to highlight the particularity of the nursing care in PED and to increase the detection of the mental suffering in the male adolescents.

LONG-TERM LIVER INVOLVEMENT IN METHYLMALONIC AND PROPIONIC ACIDEMIAS

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Background
Patients affected with methylmalonic (MMA) and propionic acidemias (PA) exhibit various long-term complications such as cardiomyopathy, renal failure and poor neurological outcome. Until now, hepatic impairment has never been described. The aim of this study was to characterize and extensively evaluate liver involvement in MMA and PA patients.

Patients and methods
We retrospectively collected clinical, biochemical and liver ultrasound data from patients with MMA (N=11) and PA (N=15) from 2003 to 2013.

Results
Alpha-fetoprotein (αFP) concentrations were elevated in 67% and 45% of PA and MMA patients respectively and tend to increase with age. Hepatomegaly (88 and 17 %) and liver hyperechogenicity was disclosed by liver ultrasound in 88% of PA and 50% of MMA patients. Frequency of liver impairment was higher in neonatal onset forms of PA.

Discussion
The mechanism of the liver damage expressed as a chronic liver fibrosis/cirrhosis observed in our patients is not fully understood. The increase of αFP with age suggests a mechanism of progressive toxicity, which could be due the metabolites that accumulate in PA and MMA. These metabolites (e.g. methylmalonic acid, propionic acid, propionylcarnitine) have already been reported to have mitochondrial toxicity as confirmed by the results in two of our MMA patients.

Extensive characterization of 14 CblC (Cobalamin C)-defective patients: clinical signs and neurocognitive outcome, biological, molecular and ophthalmologic findings

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Objectives
We retrospectively report clinical, biological, ophthalmological and outcome findings in 14 CblC patients (5 females, 9 males) with *MMACHC* mutations.

Patients and Results
The age of presentation varied from 7 days to 20 years. Time between first symptoms and diagnosis ranged from 2 days to 1 year. Six patients had neonatal onset, 6 between age 1 month and 1 year and 2 at early adult age. Two patients died before 4 months of age. Age at final evaluation ranged from 1 year to 32 years. Hypotonia, feeding difficulties, failure to thrive, nystagmus and bicytopenia with macrocytic anemia were the more frequent symptoms at initial presentation in neonatal and early onset forms. Other less common symptoms (< 50%) were HUS, hypertension, liver disease, cardiomyopathy, interstitial pneumopathy and hypothermia. All patients exhibited hallmarks of defective remethylation at diagnosis. All neonatal and early-onset patients presented abnormal ophthalmological findings. Characteristic maculopathy was present in 43% of patients and diffuse retinopathy in 50%. Neurocognitive outcome was poor with intellectual disability ranking between mild to severe for 85% of patients.

Conclusion
While marked hematological and metabolic response was observed with treatment including parenteral hydroxocobalamin, the neurocognitive outcome and ophthalmological outcome worsened independent from therapy.

Burden of *S. pneumoniae* sepsis among children included in the Swiss Pediatric Sepsis Study (SPSS)

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Introduction: Invasive pneumococcal disease (IPD) remains a burden worldwide. While adequate vaccination coverage with 7 and 13-valent conjugate pneumococcal vaccine (PCV) resulted in a 71% decrease in vaccine-type invasive pneumococcal disease (IPD) in children, less is known about other correlates of disease severity. The occurrence of severe sepsis warrants a better delineation between risk factors associated with severe outcomes from IPD.

Methods: Observational retrospective multicentered study in children under 17 years of age hospitalized with pneumococcal sepsis defined as SIRS with documented *S. pneumoniae* bacteremia between 2011-2014. Standard descriptive and comparative statistics were performed on categorical variables and subgroups while multivariable logistic models addressed the correlation between clinical and socio-demographic variables and pneumococcal severe sepsis.

Results: Preliminary data from the Swiss Pediatric Sepsis Study (SPSS), which enrolled 993 children with documented bacteremia since 2011. 109 of these patients presented with *S. pneumoniae* bacteremia. Among them, 24 (22%) patients presented severe sepsis (bacteriemia and ≥ 1 organ dysfonction), 40 (37%) patients were admitted to the ICU, 12 (11%) requiring invasive ventilation and 8 (7%) died. From the 86 children eligible for pneumococcal vaccination (which excluded 20 children born before 2006 and 7 infants under 2 months of age), a total of 66 (77%) children were vaccinated with either PCV 7 or 13. Among these, 23 (23%) were adequately vaccinated with PCV 13 and 26 (26%) with PCV 7. Multivariable analyses are currently ongoing.

Conclusions: IPD disease remains a significant burden in Switzerland despite the introduction of PCV 13 since 2011. We hope that multivariable analyses will better delineate some risk factors associated with severe sepsis and admission to the ICU (younger age and serotype replacement) and thus identify specific targets for *S. pneumoniae* prevention strategies. Future studies should also look into host genetic polymorphisms as additional correlates of pneumococcal severe sepsis.

LA CULTURE DE RECHERCHE DES INFIRMIÈRES D'UN DEPARTEMENT DE PEDIATRIE D'UN HÒPITAL UNIVERSITAIRE DE SUISSE ROMANDE

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La recherche en soins contribue à l'amélioration des soins de santé, des résultats aux patients et de la satisfaction des infirmières au travail. De plus, elle répond à des exigences sociétales et légales. Néanmoins, les résultats de recherche sont encore peu utilisés dans la pratique.

Le but de la présente étude était de définir la culture de recherche chez les infirmières travaillant au sein d'un département pédiatrique universitaire en Suisse. L'enquête effectuée pour la réalisation de cette étude descriptive et corrélationnelle s'est basée sur un auto-questionnaire online explorant les connaissances, les attitudes et l'utilisation de la recherche par les infirmières ainsi que les barrières et éléments facilitant la lecture et la conduite de recherche.

Les résultats des analyses descriptives et corrélationnelles montrent que les infirmières sont intéressées à la recherche. Sur les 201 infirmières ayant répondu au questionnaire (taux de réponse 41%), la moitié a participé à des actions de promotion de la recherche, un tiers lit régulièrement des articles de recherche, 11.3% utilise souvent les résultats de recherche pour construire des protocoles de soins ou prendre des décisions cliniques. Les attitudes envers la recherche sont bonnes, elles la considèrent comme indispensable pour développer les soins. Les principales barrières relevées sont le manque de temps, de conviction, de soutien et de connaissances. Les éléments facilitant sont la formation et la motivation personnelle.

Conclusion: Malgré des attitudes positives envers la recherche, il subsiste une sous-utilisation des résultats de recherche dans la pratique des soins. Les barrières et les éléments facilitant identifiés démontrent un important besoin en temps et en formation. Les liens avec les chercheurs, déjà bien présents au travers du partenariat existant au sein du département, se doivent d'être renforcés et mis en lumière par une présence plus régulière aux colloques et la mise en place d'ateliers ou de journal-clubs.

Remerciements:
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Nystagmus, visual deficit and learning disorders associated with in utero methadone exposure

Jequier Gygax M, Pizzo R, Mayor-Dubois C, Maeder P, Borruat FX, Roulet-Perez E

Introduction:
Substitute methadone, as the recommended treatment for opioid-dependent women, is associated with developmental difficulties (Johnson HL 1982, McGLone 2015), and since recently is recognized as having a detrimental impact on infant visual development (McGlone 2009, 2014).

Method:
We present the case of a 10-year old girl who presented with learning disorders, horizontal nystagmus since she was 12 month-old, strabismus and low visual acuity. Except in uteromethadone exposure from conception to term, her perinatal and somatic history was uneventful, in particular no infection, no neonatal abstinence syndrome; neurological examination was normal. We performed a neuropsychological (NP) and neuro-ophthalmological (NO) examination, and a cerebral MRI.

Results:
The NP examination showed reading learning delay, visuo-spatial disorder and a visuoperceptive trouble. A bilateral optic atrophic neuropathy, an horizontal nystagmus, a strabismus with hyperopia astigmatism and diminished visual acuity (60% binocular with correction) were confirmed by the NO examination. Cerebral MRI showed optic nerve hypoplasia. Visual learning supports and adaptations improved her reading skills, allowing her to follow an age-matched school-learning program in one year.

Conclusion:
Our hypothesis is that in-utero methadone exposure impaired visual development in our patient, and led to hypermetropic astigmatism, strabismus, horizontal latent nystagmus and bilateral optic neuropathy, similar to signs and symptoms reported in case series and recent prospective studies (Gaillard and Borruat 2001; Gupta m 2012, McGlone et al 2014). Myelination impairment is one of the suspected methadone toxicity mechanisms (Velstal-Laborde 2014). Follow-up of these children is indicated as visual development disorder can confound other neurodevelopmental difficulties.

Conditions de mise en place d'une consultation infirmière dans un service d'urgences pédiatriques universitaire.

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Contexte :

Le service d'urgences pédiatriques médico-chirurgical du CHUV (Centre hospitalier Universitaire vaudois) de Lausanne accueille 35'000 enfants par an âgés de 1 jour à 18 ans. Une consultation infirmière a été mise en place en janvier 2013 avec pour objectif principal de diminuer le délai d'attente de consultations des patients aux urgences dans le cadre du plan stratégique de l'établissement.

Synthèse des éléments principaux :

- Mise en place du cadre légal à partir de la Loi Vaudoise sur la Santé Publique, de la direction des soins, de la direction médicale et du département juridique de l'établissement
- La consultation infirmière reste sous délégation médicale
- Critères de sélection : des Infirmières expérimentées en soins d'urgence pédiatriques et volontaires
- Formation préalable reçue : 6 mois de formation sur le terrain avec une validation finale des compétences acquises.
- Population cible : Tri 5 du score ATS (Australasian Triage Score), patients âgés de 3 ans révolus ne présentant pas de signes de gravité, consultant pour une pathologie ORL ou une pathologie commune simple.
- Les patients sont sélectionnés après avoir été triés. Lorsque l'infirmière le juge nécessaire, elle peut faire appel à tout moment à un médecin.
- Ordonnance sous délégation médicale (antipyrétiques, antalgiques, antibiotiques de base)
- Rapport de consultation infirmière transmis au pédiatre

Références Bibliographiques :

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Mots clefs : Consultation infirmière, urgence, pédiatrique, autonome

Démarche de réflexion autour de l'utilisation de l'Emla© et de différents sprays lors de la prise de sang en pédiatrie

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Master ès Sciences en sciences infirmières

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Introduction : les ponctions veineuses sont douloureuses et anxiogènes pour les enfants et exigent une approche préventive de la douleur. A cet égard, l'utilisation de l'Emla© a démontré son efficacité, mais ce produit requiert un délai d'attente d'une heure pour obtenir un effet anesthésiant (1–4) et il entraîne une vasoconstriction transitoire (5). Par conséquent, dans le contexte des prises de sang non programmées, les soignants de la policlinique pédiatrique du CHUV ont régulièrement recours à la Xylocaïne© 10% et à l'Aethylchlorid Sintetica©, comme alternatives à l'Emla©. Or, l'efficacité et l'indication de ces produits sont discutables. D'autres méthodes efficaces dans ce contexte existent, telle que la distraction (2,6–11).

Objectif : faire émerger une réflexion critique chez les soignants de la policlinique pédiatrique du CHUV sur les approches antalgiques existantes et leur utilisation lors de prises de sang non programmées.

Méthodologie : ce projet se base sur la méthodologie du modèle de Lescarbeau, Payette et Arnaud (12) et ses six étapes. Les pratiques cliniques du service ont été analysées en regard des recommandations issues de la littérature et de l'avis d'experts.

Résultats : la majorité de l'équipe utilise l'Emla® lors de prises de sang non programmées comme recommandé dans la littérature et par les experts. La plupart des soignants ayant recours à la Xylocaïne® 10% et l'Aethylchlorid Sintetica®, jugent leur efficacité médiocre et les utilisent davantage pour détourner l'attention de l'enfant que pour leur propriété antalgique. L'utilisation de ces produits n'est pas recommandée par les experts ni par la littérature (13). L'équipe soignante n'utilise pas de manière systématique la distraction malgré les recommandations de littérature (2,6–11) et des experts. La distraction parentale est quant à elle, systématiquement utilisée par l'équipe.
Conclusion : les résultats ont permis de proposer à l'équipe des pistes de solution pour permettre l'émergence d'une réflexion critique chez les soignants sur les approches antalgiques existantes et leur utilisation lors de prises de sang non programmées. Deux priorités d'action seront choisies afin de réaliser ce projet.

Utilisation et efficacité d'un cartable numérique chez des élèves présentant un handicap moteur

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Contexte :
Le cartable numérique est un outil permettant aux enfants en situation d'handicap de pouvoir aller à l'école avec des outils informatiques complémentaires ou qui se substituent aux outils se trouvant au sein d'un cartable d'écolier. Les objectifs de cette étude étaient d'investiguer l'utilisation et l'efficacité de de cet outil du point de vue d'enfants atteints par un handicap moteur, ainsi que d'identifier de potentiels facteurs de réussite ou d'échec du projet.

Méthode :
Des entretiens semi-structurés ont été réalisés, afin de développer un questionnaire online. Ce dernier a été envoyé par mail aux utilisateurs inscrits dans la bibliothèque numérique de Defitech, ainsi qu'à des élèves fréquentant une école spécialisée.

Résultats :
Le cartable numérique était utilisé principalement pour la production écrite. Il semblait être bien intégré par les professeurs ainsi que les camarades de classe. Seul l'accès à internet n'a pas été disponible pour tous les élèves, pouvant engendrer sa sous-utilisation. Du point de vue de l'efficacité, la majorité des utilisateurs ont vu un gain dans la quantité et la qualité de leur production écrite, ainsi que dans l'autonomie, l'estime de soi et ont vu une réduction de l'effort dédié à la réalisation d'une activité scolaire. Ils ont vu également un gain de nouvelles compétences acquises grâce à l'ordinateur. Un apprentissage suffisant du cartable numérique, ainsi qu'un environnement scolaire favorable à son intégration, ont été deux facteurs contribuant à la réussite du projet.

Conclusion :
Le cartable numérique constitue un outil efficace en termes d'activités scolaires, mais aussi en termes de participation, d'autonomie et de réduction de l'effort dédié aux activités scolaires. Un profil de candidat optimal n'a pas pu être établi, indiquant que cet outil pourrait être pertinent dans diverses formes de handicap moteur.

Participation aux soins des parents d'enfants hospitalisés en pédiatrie

Julia Rohner Abdoul → absente le 04.02.2015

Infirmière CHUV

Introduction
La majorité des parents souhaitent être présents lors de l'hospitalisation de leurs enfants et participer à leurs soins. Cette participation aux soins de bases ou techniques peut être passive ou active. La participation aux soins des parents nécessite une communication efficace entre les parents et les soignants, élément clé d'un partenariat centré sur la famille. Le cadre théorique du « partnership with parents » a guidé cette étude.

But de l'étude
Connaître les besoins des parents quant à leur participation dans les soins de leur enfant hospitalisé.

Devis
L'étude est descriptive simple

Méthode
Après l'acceptation institutionnelle de l'étude, la collecte des données a duré quatre mois dans trois services pédiatriques d'un centre hospitalier universitaire en Suisse romande. La participation parentale aux soins de leur enfant a été mesurée à l'aide des questionnaires Participation aux Soins des Parents (PSP) et EMpowerment of PArents in THe Intensive Care (EMPATHIC-30©).

Résultats
Sur 184 questionnaires distribués, 82 ont été analysés (44,6% de taux de réponse). En moyenne pour tous les items, la proportion de participation des parents est de 90,0 (éT=8,0) pour les soins passifs, 84,5 (éT=6,8) pour les soins de bases et 53,8 (éT=13,2) pour les soins techniques. Ils trouvent important et se sentent libres de participer aux soins. Cependant, d'avantage d'informations pourraient être utiles pour renforcer cette participation. Les participants sont satisfaits de leur participation, mais constatent une moins bonne attention portée à leur égard par les soignants lors de l'hospitalisation de leur enfant (M=4,2, éT=0,2).

Conclusions
Cette étude a démontré que, dans les unités investiguées, les parents sont satisfaits de leur participation aux soins. Néanmoins, la communication avec les soignants pourrait être favorisée et améliorée.

Implication pour la pratique
La participation aux soins devrait être discutée systématiquement et régulièrement entre parents et soignants, en mettant en avant l'importance d'une communication efficace.

Remerciements
Un grand merci aux parents ayants répondus au questionnaire, aux personnes qui m'ont encadré pour ce travail, Mme Ramelet, Mme Vannay et Mme Grandjean. A ma famille et mes proches qui ont été d'un soutien indispensable durant la formation.

Cette étude est réalisée dans le cadre la formation Master ès Sciences en sciences infirmières UNIL – HES-SO dispensée par l'Institut Universitaire de Recherche et de Formation en Soins (IUFRS).

Low Incidence of Severe Hyperbilirubinemia in Switzerland: but it could be better!

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Introduction
Severe hyperbilirubinemia is the most common cause of neonatal hospital readmissions. It can lead to an acute encephalopathy and potentially to kernicterus with persistent neurodevelopmental sequels. Early discharge from nurseries and a lack of follow-up of the jaundiced infants seem to be the major causes for a surge in recent years. This nationwide, population based, prospective study aimed to determine incidence and aetiology of severe hyperbilirubinemia in term and late preterm infants in Switzerland.

Materials and methods
Prospective study over 5 years (2007 -2011) in collaboration with all 33 paediatric hospitals in Switzerland, the Swiss Paediatric Surveillance Unit and the Swiss Federal Offices of Statistics and of Public Health. An anonymous, two step reporting system was used with a check-off form and a secondarily sent detailed questionnaire. All newborn infants with gestational age (GA) ≥35 weeks with at least one value of total serum bilirubin (TSB) exceeding the age specific exchange transfusion limit (ETL) were included.

Results
During the study period, 379'280 live births (LB) with GA ≥35 weeks were recorded in Switzerland of which 129 developed severe hyperbilirubinemia (incidence: 34.0/100'000 LB). Preterm infants (>200/100'000 preterm LB) and boys (65.9%) were overrepresented. Incidence of very high TSB peaks (>514 µmol/L; >30 mg/dL) was 1.8/100'000 LB. The aetiology was identified in 63 cases (58.8%) of which 58 were related to blood group incompatibility (ABO: 63.6%; Rhesus and subgroups: 24.3%) and 3 cases to severe hematoma (4.5%). The first TSB measurement was performed within the first 12h only in 9.6%, although the risk factors (mother's blood group and hematoma) were known at birth. In 54 (43.2%) of the 125 patients with available data, the first bilirubin measurement was already above the ETL. In 16 (29.6%) of these cases, the first TSB was measured only >12h after first notice of jaundice.

Conclusions
The incidence of severe hyperbilirubinemia in Switzerland is lower than those reported in other countries. However, many of the recorded cases could have been avoided by a better recognition of the risk factors and an earlier measurement of TSB. In many cases, there is a delay between recognized clinical jaundice and first TSB measurement.

Blunt pancreatic trauma in children: diagnosis and nonoperative management

Claire-Anne Saugy

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***Background**:* Nowadays, pancreatic pediatric traumas are infrequent and remain difficult to diagnose and manage especially in the most serious cases: should we operate or not? In the University Hospital Center of Vaud (CHUV), since 1999, all but one pancreatic trauma were nonoperatively managed whatever the severity score was. The aims of this retrospective study are to report methods of diagnosis and nonoperative management we applied and to compare them with data from literature, in order to define the best approach of these traumas.

***Methods**:* We reviewed medical records of 14 children (2-15 years), all nonoperatively treated for pancreatic injury in the CHUV between 1999 and 2012. Traumas' severity is classified in two groups according to the Moore's score: the low-grade's (I-II) and the high-grade's (III- IV). Diagnosis is based on lesions on imagery and/or pathological pancreatic enzymatic levels (≥ 3 times the standards) during hospitalization. We recorded medics, nutrition's modalities, biology and pancreatic complications.

***Results**:* All traumas were blunt. 7/14 children had high-grade traumas. 2/7 children with low-grade's never reached pathological enzymatic levels. Lipase was more sensitive and specific than amylase. Initial US missed twelve lesions. Initial CT showed 9/14 pancreatic traumas but missed 4/7 low-grade's. 10/14 patients received antibiotics according unclear modalities. 8/14 benefited from total parenteral nutrition (median 7days (5-21)). 3/14 patients developed pseudocysts, all appearing during the first week. 2/3 spontaneously resolved. 2/6 patients treated with somatostatin analogs developed pseudocysts. Median length of hospitalization was 19,5 days (4-43). No mortality and major morbidity were seen.

***Conclusion**:* Nonoperative care of grades I-IV pancreatic traumas seems to be sure and effective. However, methods of diagnosis have some limitations and management still need to be improved.
Keywords: pancreas, trauma, children, nonoperative management

Investigations of the mechanisms that regulate the differentiation of newborn monocyte under M1 and M2 polarizing conditions

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Keywords. M1/M2 macrophages, newborns, innate immunity

Background
Newborns are highly susceptible to infections due to the immaturity of their immune system. During the first week of life, 1-5/1000 infants suffer from early-onset neonatal sepsis with high morbidity and mortality. Depending on the environment to which they are exposed, monocytes can turn into M1 or M2 macrophages with pro-inflammatory or anti-inflammatory and tissue repair properties, respectively. Our aim is to define whether the differentiation of monocytes into M1/M2 macrophages is altered in newborns when compared to adults.

Methods
Monocytes were isolated by positive selection from umbilical cord blood mononuclear cells of healthy term newborns and from PBMCs of adult volunteers (n=20 of each). Monocytes were incubated for 7 days with GM-CSF or M-CSF to induce M1 or M2 polarization, respectively. M1/M2 macrophages were exposed for 20h to LPS. Cytokine production was quantified by RT-PCR and ELISA and activation of signaling pathways were analyzed by Western blotting.

Results
Newborn M1 macrophages produced lower levels of TNF and IL-12p70 than adult M1 macrophages, whereas newborn and adult M2 macrophages produced similar levels of IL-10 after LPS stimulation. In agreement, lower mRNA levels of IL-12p35 and IL-23p19 were detected in newborn M1 macrophages after stimulation.

Conclusions
Our results suggest that monocyte to M1 macrophage differentiation is impaired in newborns, which may weaken innate immune responses to infection. Additional cytokines, polarization markers, and transcription factors are being analyzed to further unravel the specificities of the differentiation program of newborn monocytes under M1/M2 polarizing conditions.

Application de la PCIME aux enfants atteints de déshydratation dans un service d'urgence de pays développé

Michel Schneider

étudiant

→ A RACCOURCIR

Situation

La PCIME (Prise en Charge Intégrée des Maladies de l'Enfant) est une stratégie médicale mise en place par L'OMS et l'UNICEF afin d'améliorer la prise en charge des maladies à haute mortalité dans les pays du Sud comme les pneumopathies, la malaria, la diarrhée, la malnutrition et la rougeole qui sont les 5 principales causes de décès chez les enfants de moins de 5 ans (70%). La PCIME est aujourd'hui introduite dans plus de 75 pays.

Justification

Au cours d'une période d'observation, plusieurs éléments au sein du service des urgences de l'HEL comme une classification parfois floue ou non-établie sur les critères de l'OMS ainsi que des désaccords entre médecins et infirmiers concernant le stade de déshydratation ont été constatés. Dans ce contexte, l'introduction de la PCIME permettrait typiquement d'apporter des solutions à ce type de problématique. La PCIME basée sue l'EBM a fait ses preuves dans les pays du Sud mais les donnée manquent dans les pays dis développés.

Objectif

1. Evaluer la mise en pratique de la PCIME dans un service d'urgences pédiatriques d'un pays développé (HEL)
2. Evaluer le degré de concordance médico-infirmier sur le stade de déshydratation des enfants se présentant avec une diarrhée.

Méthodologie

L'étude s'est déroulée sur un mois et les données étaient recueillies à l'aide de 3 moyens :

1. Fiche de recueil durant les évaluations médicales (MA) et infirmières (INF)
2. Questionnaire aux parents
3. Tableau de comparaison des signes de DH

Au milieu du mois, un cours d'introduction à la PCIME spécifique aux diarrhées et aux déshydratations a été donné. Les médecins assistants ont également analysé et discuté des vidéos d'enfants déshydratés à différentes stades (A, B ou C selon l'OMS). Les données recueillies avant et après la formation ont été comparées.

Résultats escomptés

Une amélioration de la qualité de prise en charge des enfants atteints de diarrhées était attendue. Découlant de ce point, une meilleure compréhension de la maladie par les parents ainsi qu'une diminution des reconsultations inutiles ou trop tardives devaient également être constatée.

Résultats

La grille de recueil des données montre des améliorations à différents niveaux. Nous citerons ici, le score moyen de l'anamnèse, certains items comme la notion d'un voyage récent, la présence de sang dans les selles et le test du pli cutané. D'autres éléments comme la description de l'état neurologique de l'enfant, l'enfoncement des yeux et la réalisation d'un examen clinique complet étaient élevés à la base et sont restés stables au cours de l'étude. Cependant, malgré la formation PCIME, le « test de la soif » ainsi que des éléments de l'anamnèse concernant le risque d'infection sévère ont montré une diminution de leur performance.
Le questionnaire des parents révèle que les parents se sentent généralement capable de préparer les SRO et qu'ils sont régulièrement avisés de reconsulter en cas de persistance de la fièvre et des diarrhées. D'autres motifs de reconsultation ne sont en revanche pas toujours expliqués aux parents et les brochures d'explications ne sont pas systématiquement distribuées.
La concordance médico-infirmière est difficilement évaluable car aucun enfant n'a présenté des signes de déshydratation avancée ce qui lmite le risque de divergence d'avis.

Interprétation

Plusieurs éléments limitent la validité générale de nos conclusions. Les principaux sont la petite taille de l'échantillon et la courte période d'observation. Le temps de formation est également insuffisant et seule une moindre partie du personnel infirmier en a bénéficié. Le contexte socio-culturel et complètement différent des pays du tiers-monde. Néanmois, les trois volets de la PCIME ont été évalués dans cette recherche et nous pouvons affirmer que tous sont potentiellement améliorables dans ce service d'urgence. En sensibilisant d'avantage les soigants à la recherche des quatres critères des l'OMS pour la déshydratation et à la catégorisation correcte des enfants dans les plans A, B ou C, les compétences des soignants peuvent encore se renforcer. Les compétences de la communauté peuvent également s'accroitre en divulgant de meilleurs conseils aux parents pour le retour à domicile et en leur expliquant mieux la maladie. Le troisième volet concernant le système de santé global pourrait être renforcé en organisant mieux le service afin que chaque parent reçoive une brochure en fin de consultation et en remplissant plus régulièrement le carnet de santé.

Mots-clés : PCIME - IMCI - OMS – Diarrhées – Pédiatrie

Necrotizing pneumonia in children: radiological aspect and comparison of CT vs US

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Background
Necrotizing pneumonia (NP) is characterized by the development of necrosis within an infected lung. It has been increasingly reported in children. The aim of our study was to describe the typical radiological aspect of NP and to investigate the respective role of CT and US in the diagnosis and management of the disease.

Material and Methods
We retrospectively reviewed 39 patients (male: 21; female: 18; mean age: 4.2 years old) with NP treated in our institution between 01/01/2000 and 30/06/2015. The radiological features assessed included: location and aspect of the consolidations (parenchymal enhancement), presence of pleural effusion, atelectasis and pneumothorax. Clinical features such as: type of bacteria, presence of fever, need of O2 and duration of hospitalization were also considered.

Results
Every patient had a mean of 15 x-rays, 1.3 US and 2 CT. On CT, consolidations were heterogeneous in 97.5% of the patients. This correlated well with US findings when available (N=20). On CT, 85% of the patients had a pleural effusion of which, a fifth were loculated. 82.5% complicated by cavitation and 17.5 % by bronchopleural fistula. Adenopathies were present in only 25% of the cases.

Conclusion
Both US and CT were complementary in the diagnosis and in the treatment of NP. On one hand, CT helped in the diagnosis of early necrosis and to evaluate its extension. CT was mandatory to detect bronchopleural fistulae. On the other hand, US was useful in the follow up of lung necrosis and to assess the evolution of pleural effusion. The mean number of x-rays and CT per patient seems to be high, further work is necessary to investigate this.

Assurer une continuité des soins dans la transition des services pédiatriques vers les services adultes : évaluation du rôle des soins infirmiers pour le diabète de type 1

ME Verga*, S Zoni*, MP Aquarone-Vaucher, A Dwyer, T Gyuriga, M Hauschild, AS Ramelet

Introduction : Le diabète type 1 est une maladie chronique souvent diagnostiquée durant l'enfance. A l'atteinte de la majorité, les jeunes sont amenés à quitter les services pédiatriques pour les services adultes ce qui génère incertitude et angoisse. Ce transfère comporte un risque élevé de rupture de soins et de complications. La consultation de transition infirmière pour le diabète de type 1 du canton de Vaud, soutenu par le programme cantonal diabète Vaud, a pour but d'assurer la continuité de soins. Cette étude vise à évaluer l'importance de l'accompagnement et du soutien lors de cette consultation à travers l'évaluation de la satisfaction des jeunes qui y sont suivis, ainsi que l'influence de cette consultation sur leurs résultats de santé.

Méthode : Etude descriptive transversale en cours. 58 jeunes suivis à la consultation de transition infirmière ont été contactés. Un questionnaire d'évaluation de l'adhérence au traitement thérapeutique et trois questionnaires traitant de leur perception de la relation avec l'infirmière de transition sont actuellement récoltés. La valeur de l'hémoglobine glyquée sera obtenue auprès des diabétologues traitants.

Résultats : Les résultats attendus sont relatifs à l'importance et à la fréquence des facteurs de la relation, à la satisfaction avec l'intervention, ainsi qu'à l'adhérence au traitement et à la stabilité de l'hémoglobine glyquée dans les valeurs proche d'un diabète contrôlé.

Conclusion : Cette étude permettra une meilleure compréhension de l'importance de la relation de soins avec une infirmière dans le processus de transition ainsi que son influence sur les résultats de santé des jeunes qui y sont suivis.

Remerciements : Cette étude est conduite dans le cadre la formation au Master ès Sciences en sciences infirmières et soutenue par le département médico-chirurgical de pédiatrie (DMCP).

La satisfaction des parents lors de l'hospitalisation de leur enfant aux soins continus de pédiatrie

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Contexte. L'évaluation de la satisfaction des parents concernant la pratique de soins centrés sur la famille permet d'élucider l'adéquation entre les soins fournis et les attentes parentales.
Toutefois, les outils évaluant ce concept à ce jour, peinent à prendre en compte l'expérience des patients et des parents et sont rarement spécifiques au contexte de soins, ce qui limite l'utilisation des résultats. De plus, malgré un développement accru des unités de soins continus, il existe peu de littérature à ce sujet.

Buts. Cette étude descriptive teste la pertinence de l'utilisation de la version française du questionnaire EMPATHIC-30© aux soins continus et évalue la satisfaction parentale liée aux soins prodigués lors de l'hospitalisation de leur enfant.

Méthode. Le questionnaire EMPATHIC-30© comprend 30 items d'évaluation de la satisfaction en lien avec la pratique de soins centrés sur la famille qui s'évaluent sur une échelle de 1 à 6 et pour lesquels la valeur attendue est de 5. Après avoir été adapté pour les soins continus, il a été distribué à tous les parents francophones dont l'enfant était transféré hors de l'unité des soins continus.

Résultats. Avec un taux de participation de 70% (n= 124), la pertinence de l'utilisation de l'EMPATHIC-30© aux soins continus est confirmée au travers des tests psychométriques effectués. Les moyennes des scores de satisfaction parentale se situent entre 5,56 (*ÉT* 0,60) pour l'attitude professionnelle et 5,16 (*ÉT* 0,69) pour l'organisation. Vingt-trois items sur 30 ont une moyenne supérieure à la valeur attendue de satisfaction parentale. Néanmoins, l'inclusion des parents dans la prise en soins de leur enfant, l'accès à l'information ainsi que l'organisation du service pourraient être améliorés. Les provenances hospitalières des enfants n'influencent statistiquement pas la satisfaction des parents.

Conclusion. Le questionnaire est prometteur et la satisfaction des parents ayant un enfant hospitalisé aux soins continus est très bonne

Physicians' attitudes faced with life threatening events in children with profound neurological disabilities

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Background
Children with profound neurological disabilities are at risk of life threatening events, especially related to respiratory morbidity. Taking decisions in these acute situations faces physicians with complex medical, ethical and judicial issues.

Aim
To assess the attitudes of Swiss physicians when faced with life threatening events in children with profound neurological disabilities.

Method
An online survey was sent to paediatric neurologists, physiatrists and intensive care specialists in tertiary centres (with child ICU facilities) in Switzerland. The questionnaire included personal characteristics, and explored participants' attitudes in life threatening situations in 2 scenarios: a. a child in minimal consciousness state (MCS); b. an infant with SMA type I. Responses were graded on a 4-point Likert scale from total agreement to total disagreement.

Result
52/95 physicians took part (55% participation). In both scenarios there was a consensus between physicians for the following attitudes: 1) favouring non-invasive ventilation, 2) favouring comfort care, 3) avoiding tracheotomy and long term invasive ventilation.

In the MCS scenario 61% of participants opposed complete cardiopulmonary resuscitation (CPR), 39% supported it. In the SMA I scenario 51% opposed complete cardiopulmonary resuscitation (CPR), 49% supported it. In the SMA I scenario if parents requested tracheotomy with long term ventilation based on religious grounds, 50% participants agreed with the attitude.

Physicians with > 20-year experience were significantly more opposed to complete CPR and favoured non-invasive attitudes. Physicians from French-speaking Switzerland were significantly more prone to withholding/withdrawing life support than their Germanspeaking peers.

Conclusion
Physicians' attitudes differ significantly, influenced by personal and cultural factors. This highlights the importance of codified multidisciplinary processes to approach these complex situations.

Compound heterozygote *CHD7* mutations in a female with Kallmann syndrome and CHARGE features

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Background
Kallmann syndrome (KS) is a rare genetic disorder characterized by anosmia and hypogonadotropic hypogonadism with absent puberty and infertility. KS associated phenotypes, such as cleft lip/palate and sensorineural hearing loss, are also encountered in CHARGE syndrome. The two syndromes overlap genetically, as heterozygous *CHD7* mutations are found in both (6% of KS and 60% of CHARGE cases).

Clinical case
The elder daughter of two healthy and unrelated Hungarian parents consulted at age 18 for absent puberty, primary amenorrhea and anosmia. She had cleft lip and palate, mitral valve prolapse, bronchial stenosis, unilateral renal hypoplasia, sensorineural hearing loss, scoliosis and bilateral synkinesia. Hormonal profile revealed isolated hypogonadotropic hypogonadism and anosmia was confirmed by formal testing, leading to the diagnosis of KS. Hypogonadism, deafness, and heart defects are CHARGE features, yet the patient does not fully meet the diagnostic criteria for CHARGE syndrome. Notably, her younger sister also has KS with mitral valve prolapse, scoliosis and synkinesia.
Whole-exome sequencing revealed a novel heterozygous mutation in *CHD7* (p.A1107V) in both KS sisters, inherited from their mother. The alanine 1107 recidue is located in the CHD7 helicase domain, and A1107V is predicted to be deleterious by 6/6 algorithms (SIFT, Polyphen-2, Mutation Taster, Mutation Assessor, LRT and FATHMM). The proband inherited an additional mutation in *CHD7* (p.M340V) from her father. The M340V variant is rare (minor allele frequency 0.6%, ExAC) and predicted to be deleterious by 2/6 algorithms.

Conclusion
To our knowledge, this is the first report of compound heterozygous *CHD7* mutations underlying KS with CHARGE-associated phenotypes. The proband harboring the bi-allelic defect ([A1107V] + [M340V]) exhibits a more severe phenotype than her sister who has a mono-allelic defect ([A1107] + [WT]). These data suggest that the additional CHD7 M340V variant may account for the variable non-reproductive phenotypes seen in the two KS sisters.

ABSTRACTS LABO

Investigation of ADA2 role in inflammation: from clinics to the biology

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Background

We described two siblings suffering since early childhood from recurrent mucocutaneous infections by *Candida albicans* and *Staphylococcus aureus* infection associated to chronic inflammation and vasculitis with upregulation of pro-inflammatory cytokines (IL-1 [illegible] and TNF). Patients display a homozygous 22q11.1 deletion, leading to the absence of the *Interleukin-17 Receptor A* (*IL-17RA*; OMIM*605461) and the *cat-eye critical region 1* (*CECR1*; OMIM*607575) genes, respectively encoding for IL-17RA and Adenosine deaminase 2 (ADA2). Inborn errors of human IL-17 immunity highlight the crucial role of this pathway in mucocutaneous protection against *C. albicans*. Mutations in *CECR1* leading to ADA2 deficiency were recently reported in patients affected by a spectrum of vascular and inflammatory manifestations, ranging from early-onset recurrent stroke to systemic vasculopathy. Although the physiological role of ADA2 is still poorly understood, these findings may reflect a potential role for ADA2 in regulating immunity and inflammation.

Hypothesis

We hypothesize that the chronic inflammation and the cytokine profile observed in patient's monocytes are conferred by the lack of ADA2. This immunological and clinical phenotype is different from that previously reported in ADA2 mutated patients. This discrepancy could be due to difference of protein level (deletion *vs.* loss of function mutation) or lack of information on the clinical spectrum of the disease. Moreover, we wonder whether there is an interaction between IL-17RA and ADA2 in causing inflammation and susceptibility to specific pathogens.

Aims and Methods

We will restore the expression of *IL17RA* and *CECR1* on patient's monocytes by lentiviral mediated transduction and assess whether the biological phenotype is rescued. Transduction efficiency will be evaluated by looking at the proteins expression. In the patient, we will assess both pro-inflammatory cytokines production in transduced monocytes and monocytes to macrophages differentiation.

Perspectives

This approach is likely to provide a unique insight into immunological pathways and mechanisms of disease in ADA2 deficient patients and molecular evidence for a rational design of ADA2-targeting drugs and/or gene therapy. In addition, our report might elucidate the potential role of ADA2 in modulating immunity and inflammation.

Glutaric and 3-hydroxyglutaric acid production by *Gcdh*$^{-/-}$ brain cell aggregates

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Glutaric Aciduria type I (GA-I) is caused by the deficiency of the enzyme glutaryl-CoA dehydrogenase (GCDH), involved in the catabolism of the amino acids lysine, hydroxylysine and tryptophan. Due to the enzymatic defect, glutaric acid (GA) and 3-hydroxyglutaric acid (3-OHGA) accumulate in body tissues and fluids. These metabolites are thought to be produced by the brain, trapped due to limited efflux and are probably responsible for brain damage in GA-I (toxic metabolite hypothesis).

We previously studied the cerebral toxicity of these metabolites *via* their administration in 3D organotypic re-aggregated brain cells issued from wild type rat embryos. To approach the *in vivo* condition while maintaining the advantages offered by this *in vitro* model, we developed a 3D organotypic re-aggregated brain cell model issued from *Gcdh*$^{-/-}$ mouse embryos.

We discovered that aggregates composed by 100% of *Gcdh*$^{-/-}$ cells could not survive under *in vitro* conditions. Therefore, we developed *Gcdh*$^{-/-}$ brain cell aggregates with 5% residual GCDH activity by adding some wild-type cells. Accumulation of GA and 3-OHGA was seen in culture medium of *Gcdh*$^{-/-}$ aggregates while none was found in wild type at day-in-vitro 5, 8 and 14. Moreover, ammonium accumulation was observed at day-in-vitro 14 in *Gcdh*$^{-/-}$ aggregates, similarly to rat aggregates exposed to 3-OHGA. However, no significant morphological alteration was observed in *Gcdh*$^{-/-}$ aggregates.

These results obtained in *Gcdh*$^{-/-}$ brain cell aggregates are in concordance with the features observed in *Gcdh*$^{-/-}$ mice. These mice develop the biochemical phenotype of GA-I, but do not manifest the typical encephalopathic crisis seen in GA-I patients unless they are fed with a high-lysine diet. In further studies, we should challenge *Gcdh*$^{-/-}$ aggregates with a metabolic stress. Here we show that *Gcdh*$^{-/-}$ developing brain cells indeed produce GA and 3-OHGA which confirms the toxic metabolite hypothesis.

Chemokine production induced by 2-methylcitrate in 3D organotypic rat brain cell aggregates

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In a model of methylmalonic aciduria (MMAuria) using 3D rat brain cell aggregates, we recently showed that ammonium levels increased in culture medium within few hours after 2-methylcitrate (2-MCA) administration. Moreover, 2-MCA altered the morphology of developing brain cells and increased cleaved caspase-3 levels at day-in-vitro (DIV) 14. To better understand the mechanisms involved, we analyzed the time course of cytokine and chemokine production in culture medium of 3D rat brain cell aggregates exposed to 1 mM 2-MCA (DIV11 to 14), which were harvested from DIV12 to 19.

Levels of the chemokines MIP-1□, MIP-2, MCP-1, MCP-3, GRO-□ and IP-10 were increased by 2-MCA exposure. Compared to controls, the increase was most substantial on DIV15 for MIP-1□□□, MIP-2, MCP-1, MCP-3 and GRO-□□ and on DIV19 for IP-10. No significant change of cytokines was observed.

Chemokines showing a substantial increase after 2-MCA exposure are also involved in other neurodegenerative disorders. They are responsible for immune cell attraction, have anti-apoptotic properties and play an important role in CNS repair. The start of the chemokines increase on DIV15 suggests a link to the maximum of elevated cleaved caspase-3 on DIV14. Further studies are necessary to unravel the precise role of chemokines in MMAuria.

Tenascin C knockout mice: pulmonary function in newborn and adult animals.

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Background: Tenascin C (TNC) is a hexameric ECM protein largely expressed in lung during organogenesis. In adulthood, its expression is rather silent but reappears transiently in case of injury. TNC inactivation negatively affects both early and late lung development. However, a complete morphological recovery occurs in adulthood. We hypothesized that TNC-KO mice would have lower lung function capacity during lung development, contrary to adults.

Material&Methods: At the age of 5 days, 3 months, 6 months and 1 year, TNC-KO and WT (SV129) mice (Forsberg et al., 1996) were intubated (intra-tracheal) and ventilated during one hour with a high tidal volume (40 ml/kg for newborns or 25 ml/kg for adults). Pulmonary function parameters were recovered using the Flexivent rodent ventilator (Scireq Inc., Montreal, Canada). Lung tissue was collected for molecular biology and histology.

Results: At postnatal day 5, TNC-KO animals exhibited higher static compliance and A-factor (estimating the total inspiratory capacity of the lung) both before and after one hour of high tidal volume (HTV) mechanical ventilation (n=5-7). Both genotypes showed the same increase in static compliance during the ventilation. At 3 months, TNC-KO animals still exhibited a higher static compliance in basal conditions, but no more at the end of the ventilation (n=3-6). Only the WT showed an increase in static compliance during the ventilation. In all cases, no distinction could be made between TNC-KO and WT lungs in terms of basic morphology or elastin staining.

Discussion: At postnatal day 5, TNC-KO lung showed a basal difference in pulmonary function parameters, but the same response to one hour of HTV mechanical ventilation. On the opposite, at 3 months, the same basal difference was present, but TNC-KO did not respond the same to the ventilation. It is possible that despite no evident morphological difference, TNC-KO lungs were more affected by the ventilation. This could indicate an increased airway resistance or elastic resistance whose origin remains to be determined. We conclude that TNC not only has an impact on lung development but also that it lasts until adulthood.

Proc Natl Acad Sci U S A. 1996 Jun 25; 93(13):6594-9.
Skin wounds and severed nerves heal normally in mice lacking tenascin-C.
Forsberg E, Hirsch E, Fröhlich L, Meyer M, Ekblom P, Aszodi A, Werner S, Fässler R.

The ALK-F1174L activating mutation mediates the upregulation of genes close to the Myc locus in tumors derived from neural crest progenitor cells

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Introduction: The anaplastic lymphoma kinase (*ALK*) is overexpressed, mutated or amplified in most neuroblastoma (NB), a pediatric neural crest-derived embryonal tumor. The ALK-F1174L mutation mediates an enhanced activation of its downstream signaling cascade and an increased oncogenic potential relative to other ALK mutations. However the precise molecular mechanisms remain unresolved.

Aims: To identify genes and pathways activated by the ALK-F1174L mutation by comparison of the transcriptomes of tumors driven by various ALK variants.

Methods: Murine neural crest progenitor cells (JoMa1), expressing ALK-wt or the most frequent activating mutations, ALK-F1174L or ALK-R1275Q, were generated by retroviral infections. Cells were injected orthotopically in adrenal gland of athymic Swiss nude mice and the transcriptomes of the resulting tumors were analyzed by Affymetrix microarrays.

Results: As expected, tumor growth of JoMa1-ALK-F1174L cells was significantly enhanced relative to ALK-R1275Q and ALK-wt groups. Tumors transcriptome comparison revealed 881 or 478 differentially expressed genes (FC>2) between ALK-wt and ALK-F1174L or between ALK-wt and ALK-R1275Q groups, respectively. Surprisingly, ALK-F1174L and ALK-R1275Q-derived tumors displayed only 9 differentially expressed genes. Interestingly, among the 7 overexpressed genes in the ALK-F1174L group, 6 genes, including Pvt1, Mtss1, Nsmce2, are located on the chromosome 15qD1 region close to the Myc locus. While Myc was not identified in this gene list, overexpression of Myc together with Pvt1, Mtss1 and Nsmce2 was validated by qPCR in ALK-F1174L-expressing tumors, and in their derived cell lines, relative to ALK-R1275Q and ALK-wt groups. Moreover, we demonstrate that their upregulation is dependent on ALK activity.

Conclusion and perspectives: These results suggest that the strong oncogenic potential mediated by the ALK-F1174L activating mutation may be caused by the upregulation a cluster of genes located in the 15qD1 genomic region. Further work will allow us to elucidate the precise regulatory mechanisms and to clarify the respective role of these genes on tumor growth.

Investigation of TWIST1 function in neuroblastoma aggressiveness and metastasis

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Introduction: Neuroblastoma (NB) originates from aberrant differentiation of neural crest-derived sympathoadrenal progenitors. TWIST1/2 overexpression is frequent in cancer and correlates with poor prognosis across many neoplasms. TWIST1/2 are key multifunctional oncogenes promoting drug resistance, EMT, invasion, metastasis, and cancer stem cell properties. Although the role of TWIST1/2 has been relatively well studied in other settings, their implication in NB pathogenesis remains poorly understood.

Aim: To investigate the impact of TWIST1/2 expression in NB aggressiveness and dissemination potential.

Methods: TWIST1/2 expression profiles was analyzed in several published data sets of NB gene expression profiles using the 'R2: Genomics Analysis and Visualization Platform (http://r2.amc.nl)' and compared to datasets of various cancers.

Results: We observed that elevated TWIST1 expression in NB tumors is associated with poor survival, while high TWIST2 expression correlates with better prognostic in all clinical stages. Moreover, high TWIST1 expression is strongly correlated with unfavorable prognostics factors of NB, such as NMYC amplification, higher stages (III and IV), undifferentiated tumors, and patient age >18 month at diagnosis. NB tumors and cells lines express significantly higher levels of TWIST1 relative to other cancers. These observations were confirmed in a panel of 10 NB cell lines, which displayed high TWIST1 mRNA and protein expression levels, as compared to melanoma cell lines, while TWIST2 mRNA was not detectable.

Conclusion and perspectives: TWIST1 expression is elevated in NB tumors and cell lines and strongly correlates with poor survival in NB in all clinical stages. We plan to further investigate the function of TWIST1 in mediating NB aggressive phenotype using NB cell lines expressing TWIST1 or silenced for TWIST1 through CRISP/Cas9 technology. The precise involvement of TWIST1 in NB cell clonogenicity, drug resistance, maintenance of cancer stem cell properties, and metastasis will be investigated using novel and well-established *in vivo* preclinical model systems.

Aldehyde dehydrogenases (ALDH) activity plays as key role in NB aggressive behavior

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Introduction: The successful targeting of neuroblastoma (NB) associated tumor-initiating cells (TICs) is a real challenge in developing new therapeutic strategies. By combining serial neurosphere (NS) passages with gene expression profiling, we have previously identified ALDH1A2 and ALDH1A3 as potential NB-TICs markers in patient-derived xenograft (PDX) tumors. ALDH1A2, ALDH1A3, with ALDH1A1, belonging to the subfamily of ALDH1 enzymes involved in the synthesis of retinoic acid, have been identified as functional stem cell markers in various cancers.

Aim: To explore the involvement of ALDH1A isoforms and the related ALDH activity in NB aggressiveness and TICs properties.

Methods: ALDH activity and ALDH1A1/A2/A3 expression levels were measured using the ALDEFLUOR™ kit, and by real-time PCR, respectively. ALDH activity was inhibited using the specific ALDH inhibitor diethylaminobenzaldehyde (DEAB) and ALDH1A3 isoform was stably silenced through the CRISPR/Cas9 technology.

Results: We have confirmed the enrichment of ALDH1A2 and ALDH1A3 mRNA expression in NB cell lines and PDX tumor during NS-passages. NB cell lines expressed ALDH1A1 and/or ALDH1A3, but almost no ALDH1A2, while PDX tumors displayed high level of the three ALDH1 isoforms. We also observed an important but heterogenous ALDH activity in various NB cell lines and PDX tumors. Specific inhibition of ALDH activity with DEAB resulted in a strong reduction of NB cell proliferative, clonogenic, and self-renewal potentials. Moreover, it partially restored NB cells sensitivity to 4-hydroxycyclophosphamide. Finally, the specific knock-out of ALDH1A3 reduced SK-N-Be2C cell clonogenic and self-renewal capacities, but had no impact on NB1C cells.

Conclusions and perspectives: We demonstrate that ALDH activity plays a key role in the aggressive behavior of NB cells. Moreover, the impact of ALDH1A3 knock-out is cell type dependent, possibly due to the different expression levels of the three ALDH1A isoforms. Further investigations are needed to define the specific impact of other ALDH1 isoforms on NB aggressive phenotype.

Acellular collagen gel tubes for urethral regeneration, in an *in-vivo* rabbit model. A long term follow up in a multicentric study.

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Introduction:
Actual surgical procedures using existing autologous tissues for the treatment of congenital malformations or injuries of the urethra are associated, in severe cases, with frequent post-operative complications. Tissue engineered collagen tubes are a promising alternative.

Methods:
We elaborated a new double layered, double compressed, rat tail collagen based tubes with enhanced mechanical properties; thus increasing their resistance, simplifying their handling and they can be sutured. Mechanical testing proved a better resistance of those collagen tubes compared to our previous single layered technique. These tubes were used as urethral grafts and sutured after a subtotal excision of the urethra. The graft was anastomosed between the prostatic urethra and the very distal native urethra. This subtotal urethral replacement (more than 80% of the total length) was done in 20 male New Zealand white rabbits, in Lausanne (Switzerland) and Kuala Lumpur (Malaysia). The constructs were all acellular, potentially off-the-shelf and no catheter was placed postoperatively.

Results:
The animals were evaluated at 1, 3, 6, and 9 months by contrast voiding cysto-urethrography, histological examination and immunohistochemistry staining. All rabbits survived the surgical implantation. This multicentric study revealed spontaneous regrowth of urothelial cells (UC) and smooth muscle cells (SMC) in all grafts at 9 months and reduced severe postoperative complications. The Stenosis (20%) and fistulae (20%) could be potentially overcome by leaving the urinary catheter after surgery.

Conclusion:
Those novel compressed collagen gel tubes are easy to handle, can be sutured and therefore adaptable to current surgical techniques to establish the continuity between tubular anatomical structures, in particular, urethra and ureter. Therefore, they are suitable for clinical applications and may be an alternative to the existing surgical treatment.

Tissue engineered, growth factor loaded, collagen scaffolds for bladder augmentation in a rat model.

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Introduction:
Bladder augmentation is a common procedure in both adults and children in the management of different pathologies as tumor, neurogenic bladder or even post traumatic reconstruction. The current procedures using digestive patches have their limitations and complications, therefore tissue engineered collagen grafts are a promising alternative.

Methods:
We compared the mechanical, functional and cellular behavior of 5 different collagen based scaffolds, the acellular group (N=4), the cellular group (4 weeks cultured with human smooth muscle cells (SMC)) (N=4), the decellularized group (N=4), and 2 groups with different concentrations of IGF-1 (Insulin-like Growth Factor-1) (N=4 low dose and N=4 high dose). After a hemi cystectomy in a nude rat model, these collagen-based patches were sutured in place in a total of 20 rats.

Results:
A surgical success rate of 87.5 % was achieved, and was linked to the learning curve of the surgical procedure. All grafted animals showed normal bladder volumes and voiding capacity after 4 weeks. Host cells had populated all the grafts within a month. The decellularized, the cellular scaffold group and the growth factor groups showed a faster regeneration as compared to the acellular scaffold. In the growth factor groups, dose dependent cell migration and collagen degradation was observed at one month.

Conclusion:
This study shows that growth factor loaded collagen based scaffolds are a valid option for tissue engineered bladder augmentation, especially when bigger animal models will be considered. The non-cellular grafts, although slower in regeneration have the advantage to be off-the-shelf and have potentially a greater clinical application as they are technically easier to produce and are more cost effective.

KUVAN®: a treatment for Phenylketonuria with potential toxicity on developing brain cells

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Phenylketonuria (PKU) is an inborn error of phenylalanine (Phe) metabolism caused by phenylalanine hydroxylase (PAH) deficiency. PKU patients accumulate Phe in tissues and body fluids. The main symptoms are neurological damage leading to intellectual deficit and neurodegeneration. Rigorous Phe-restricted diet was the main therapeutic PKU management until KUVAN® entered the market. KUVAN® (sapropterin dihydrochloride) is a pharmaceutical version of tetrahydrobiopterine (BH4) which is a cofactor of PAH and helps in patients with residual enzyme activity to reduce Phe blood levels. This treatment is prescribed to BH4 responsive PKU patients from 4 months of age. Until today it is controversially discussed whether and to what extend Kuvan passes the blood brain barrier. Neuropsychological evaluations of our PKU patients recently revealed attention deficits with hyperactivity in patients treated with KUVAN® that significantly exceeded what is observed in patients following a classical low Phe diet. In this project we evaluated the effects of different concentrations of KUVAN® on developing brain cells in an *in vitro* model for brain damage.

3D primary reaggregated brain cell cultures derived from Sprag Dawley rat embryos on E15 were exposed to different concentrations of KUVAN® (50, 75 or 100 ng/ml) from DIV11 to DIV14 corresponding to early childhood. Changes in morphology and viability of different brain cell types were studied by immunohistochemistry. We found swollen astrocytes and a decreased number of astrocytic fibers and oligodendrocytes (100 ng/ml). Immunofluorescence staining of activated caspase-3 revealed an increased apoptosis rate for all concentrations of KUVAN®. Our preliminary results showed a significant toxicity of KUVAN® on different brain cell types in our *in vitro* model. Astrocyte swelling and altered levels of neurotransmitters are associated with attention deficit/hyperactivity disorders (ADHD). Further studies must be conducted to better understand the links and mechanisms leading to the observed effects.

Bases anatomiques de l'innervation des muscles larges dans le traitement des aplasies de coupole diaphragmatique

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Introduction : En cas d'aplasie de coupole diaphragmatique, la fermeture directe du diaphragme est impossible. Le chirurgien peut soit utiliser une prothèse non résorbable présentant un risque supérieur de récidive, d'infection, voir de trouble musculo-squelettique, soit réaliser un lambeau, notamment de muscle oblique interne (MOI) et de muscle transverse (MT), lambeau triangulaire, dont la base (axe de rotation) passe par l'extrémité médiale de K11 (EMK11) et le processus xiphoïde. Les études cliniques montrent un tonus préservé du lambeau, mais peuvent évoquer une hypotonie du muscle oblique externe (MOE) laissé en place.

Objectif : Etudier l'innervation du MOE, et du lambeau, par le 10ème nerf intercostal (10ème NIC).

Matériel et méthode : Etude anatomique de l'innervation des muscles larges de l'abdomen par le 10ème NIC (nombre de branches nerveuses, trajet, naissance en amont ou en aval l'EMK11) à partir de la dissection de 40 hémi parois thoraco-abdominales (20 droites, 20 gauches).

Résultats : Caudalement au diaphragme, le 10ème NIC est toujours situé entre le MOI et le MT. En moyenne, 9 branches innervent le MOE, 77% naissant en aval de l'EMK11. En moyenne, 9 et 12 branches innervent respectivement le MOI et le MT.

Conclusion : Cette étude confirme la bonne innervation du lambeau de MOI et de MT, en faveur d'un tonus du lambeau préservé, et en faveur de la réalisation d'un lambeau de MOI et de MT dans les aplasies de coupole diaphragmatique. Cependant 75% des branches innervant le MOE issues du 10ème NIC sont sectionnées par le prélèvement du lambeau, plaidant pour le renforcement de la paroi abdominale par la mise en place complémentaire d'une prothèse résorbable abdominale qui, par la fibrose provoquée et l'absence de rétraction des MOI et MT, limiterait le risque d'hypoplasie abdominale et ses conséquences respiratoires chez des patients présentant tous une hypoplasie pulmonaire.

Mots clés : Hernie diaphragmatique congénitale ; Aplasie de coupole diaphragmatique ; Lambeau de muscles larges ; 10ème nerf intercostal

Mutations in the heat-shock protein A9 (HSPA9) gene cause the EVEN-PLUS syndrome of congenital malformations and skeletal dysplasia.

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We and others have reported that mutations in *LONP1*, a gene coding for a mitochondrial chaperone and protease, are the cause of the human CODAS (cerebral, ocular, dental, auricular and skeletal) syndrome (MIM 600373). Here, we delineate a similar but distinct condition that shares the epiphyseal, vertebral and ocular changes of CODAS but in addition includes severe microtia, nasal hypoplasia, and other malformations, and for which we propose the name EVEN-PLUS syndrome, for epiphyseal, vertebral, ear, nose, plus associated findings.

We sequenced the exome of 2 siblings from a consanguineous family and one individual of unrelated parents. We did not find any mutation in *LONP1*. Instead, we identified rare pathogenic biallelic mutations in all 3 patients in only one gene, *HSPA9*. We found an homozygous missense (p.R126W) in the 2 siblings and compound heterozygous mutations (p.Y128C & p.V296*) in the third individual.

HSPA9 gene encodes mHSP70/mortalin, another highly conserved mitochondrial chaperone protein essential in mitochondrial protein import, folding, and degradation. The functional relationship between *LONP1* and *HSPA9* in mitochondrial protein chaperoning and the overlapping phenotypes of CODAS and EVEN-PLUS delineate a family of "mitochondrial chaperonopathies" and point to an unexplored role of mitochondrial chaperones in human embryonic morphogenesis.