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Mixed Topics 2

106
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Prevalence of long-term neurologic impairment after pediatric arterial ischemic stroke

M. Lopez[a], I. Huete[b], M. Hernandez[a]. [a]*Pediatria, Pontificia Universidad Católica de Chile, Santiago, Chile;* [b]*Radiology, Pontificia Universidad Católica de Chile, Santiago, Chile*

Background: Arterial ischemic stroke (AIS) is an emergent clinical entity in pediatrics, with a high morbidity associated.
Aim: to describe the prevalence of permanent neurological disability, mortality and recurrences after AIS on childhood, and to explore the association between outcomes and radiological variables.
Patients and methods: prospective study with a cohort of patients, aged between 30 days and 18 years at stroke, and follow-up at least 5 years in a tertiary hospital of Chile.
Results: A total of 60 children with AIS were registered prospectively by the database of Hospital PUC Registry from 2003-2008, 37 males (61,7%) and median age at stroke was 15 months (range 79). The risk factor were acute systemic condition (n = 18; 40,9%) acquired and congenital heart disease (n = 18, 40,9%) and chronic systemic condition 8n = 15; 27,3%). Fourteen patients died (23,3%). AIS recurred in 9 (14,3%).The prevalence of neurological disability was 68% (28/44), the most frequent was permanent motor deficit (63% and refractory epilepsy was 6 (16,6%).
Conclusion: Mortality and long-term neurological disabilities after pediatric arterial ischemic stroke were high. Our results show that neuroplasticity is not sufficient to minimize the disability in this population.

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107
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Neurovascular imaging is not always normal in neonatal arterial ischemic stroke

I. Siddiq[a], D. Armstrong[b], M. Moharir[a], G. deVeber[a], D. MacGregor[a], R. Askalan[a]. [a]*Paediatrics, University of Toronto, Toronto, Canada;* [b]*Diagnostic Imaging, University of Toronto, Toronto, Canada*

Background: Neonatal arterial ischemic stroke (AIS) is the most common pediatric stroke occurring in more than 1/4000 live births with a risk of recurrence of less than 1%. The presence of an arteriopathy is associated with high risk of recurrence in childhood stroke. However, the prevalence and risk factors of an arteriopathy in neonatal stroke are not known.
Objective: We sought to characterize the subgroup of neonates with AIS who have abnormal vasculature.
Patients and methods: This is a single center retrospective case-control study of patients with neonatal stroke from 1991-2012. Charts were reviewed for neonates with AIS and neuroimaging that included vascular imaging (MRI/MRA). Clinical data of patients with abnormal MRA was compared to the control group of neonates with AIS but a normal MRA.
Results: A total of 142 cases of neonatal AIS were identified of which 82 patients had MRI/MRA. Among the neonates with vascular neuroimaging, 30 had abnormal vessels (minimum prevalence rate of 36%). The majority of vascular abnormalities were stenotic or hypoplastic branches. Two patients (7%) had dissection. Young maternal age, positive maternal GBS, C-section delivery, low APGAR scores, low Hgb, and cardiac defects were significantly ($p < 0.05$) more common in neonates with abnormal vessels.
Conclusion: Neurovascular imaging is challenging in neonates so often not performed. However, we recommend that an MRA to be performed in neonates with AIS who have any of the risk factors identified in this study. Early diagnosis of their vasculopathy may change their stroke management and impact outcome.

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108
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FSD-C10 promotes oligodendrocyte fate in Experimental Autoimmune Encephalomyelitis (EAE)

Y.H. Li[a], J.J. Huang[b], J.Z. Yu[a], C.Y. Liu[a], L. Feng[a], Z. Chai[c], B.G. Xiao[d], G.X. Zhang[e], C.G. Ma[a]. [a]*Institute of Brain Science, Shanxi Datong University, Datong, China;* [b]*Department of Neurosurgery, Coalmine Group General Hospital, Datong, China;* [c]*Shanxi University of Traditional Chinese Medicine, "2011" Collaborative Innovation Center/Research Center of Neurobiology, Taiyuan, China;* [d]*Institute of Neurology Huashan Hospital, Institutes of Brain Science and State Key Laboratory of Medical Neurobiology Fudan University, Shanghai, China;* [e]*Thomas Jefferson University, Department of Neurology, Philadelphia, USA*

Background: MS is a neurodegenerative disease characterized by the progressive loss of myelin that may lead toward a chronic demyelination, impairing normal axonal conduction, ultimately causing neurodegeneration.
Objective: Fasudil, Rho kinase (ROCK) inhibitor, is known to suppress EAE, but presents several limitation such as narrow safety window and lower bioavailability. Previous study demonstrated that intranasal delivery of FSD-C10, a novel Fasudil derivative, is capable

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of ameliorating EAE. In this study, we further analyzed the effect of FSD-C10 on oligodendrocyte formation.

Material and methods: Female adult C57BL/6 mice were immunized with MOG_{35-55} to induce chronic EAE. The study was approved by the Ethics Committee of Shanxi Datong University. Mice received 10 μl/ nostril (5 μg/μl) FSD-C10 at the entrance of the nostrils on day 3 until day 27 p.i. Mice that received the same volume of ddH_2O nasally served as EAE controls.

Results: FSD-C10 inhibited proliferation of CD4, CD68 and $CD11b^+$ immune cells, caused less immune cells in brain. In contrast, FSD-C10 stimulated NG2-expressing oligodendrocyte precursor cell and GalC-expressing oligodendrocyte proliferation, causing more oligodendrocyte formation. In addition, FSD-C10 also stimulated the production of neurotrophic factors NT-3 and GDNF, shifted activated microglia from M1 to M2 phenotype and inhibited inflammatory responses in the brain.

Conclusions: These results indicate that FSD-C10 promotes oligodendrogenesis and remyelination by elevating growth factors and strengthening of the microglial neuroprotective phenotype (M2) conducive for repair. (Grant: The Department of Science and Technology, Shanxi Province of China, 2013081058; Research Project Supported by Shanxi Scholarship Council of China, 2014-7).

Keywords: oligodendrogenesis, neurotrophic factors, inflammatory responses, NG2, GalC.

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109
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Establishing a human neuronal derived-iPSC model to clarify the pathogenetic mechanism for PKAN

D. Orellana Riquelme[a], P. Santambrogio[a], A. Rubio Garrido[b], C. Cancellieri[b], P. Venco[c], S. Taverna[d], V. Tiranti[c], B. Garavaglia[e], V. Broccoli[f], S. Levi[a]. *[a]Division of Neuroscience Proteomic of Iron Metabolism Unit, Vita-Salute San Raffaele University, Milan, Italy; [b]Division of Neuroscience Stem Cells and Neurogenesis Unit, Vita-Salute San Raffaele University, Milan, Italy; [c]Unit of Molecular Neurogenetics, IRCSS Foundation Neurological Inst. C. Besta, Milan, Italy; [d]Division of Neuroscience, Vita-Salute San Raffaele University, Milan, Italy; [e]Division of Neurogenetics, IRCSS Foundation Neurological Inst. C. Besta, Milan, Italy; [f]Division of Neuroscience Stem Cells and Neurogenesis Unit, CNR-National Research Council Inst. of Neuroscience and San Raffaele Scientific Institute, Milan, Italy*

Mutations in the *PANK2* gene, which encodes pantothenate kinase 2, underlie an autosomal recessive inborn error of coenzyme A metabolism, called pantothenate kinase-associated neurodegeneration (PKAN). PKAN is characterized by dystonia, dysarthria, rigidity, retinal degeneration and severe iron accumulation in the brain. The pathogenesis mechanism of this disorder remains largely unknown. Current models recapitulate only a subset of the pathological manifestations and lack any neurological phenotype in particular the iron deposition in the brain. Considering all of this, there is the urgency of establishing meaningful experimental models to determine the pathological events leading to the disease. Toward this aim, we have employed iPS cell technology for generating an *in vitro* disease model. We have succeeded in generating derived-iPSC neurons from patients and relative healthy donors by using the Sendai reprogramming vectors. Cells were analyzed for mitochondrial functionality, oxidative status and iron metabolism. The derived-iPSC neurons display a reduced antioxidant defense, increased level of ROS development and abnormal electrophysiological properties respect to the control. Furthermore, PKAN derived neurons present electron dense aggregates inside the mitochondria of a still unknown nature. In conclusion, we succeeded in obtaining a human neuronal model to study PKAN disorder and the preliminary results indicated that PKAN derived neurons present altered oxidative status, abnormal mitochondrial functionality and morphology. The financial support of Telethon (Grant n°: GGP11088) and AISNAF is gratefully acknowledged.

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110
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Investigation of regulatory factors in Lipid Storage Myopathies (LSM) with triglyceride accumulation

C. Angelini, E. Tasca, V. Pegoraro. *Neuromuscular Center, IRCCS S.Camillo, Venice - Mestre, Italy*

Background: Triglycerides are massively stored in LSM, i.e. carnitine deficiency, RR-MADD and NLSD-M (ATGL deficiency), conversely, in CPT-II deficiency lipid droplets are almost absent.

Objective: We aimed to analyse factors that regulate degradation and *PPAR-gamma* pathways. The Transcription Factor-EB (TFEB), a master regulator of lysosomal biogenesis and autophagy, is induced by starvation through an autoregulatory feedback loop and exerts a global transcriptional control on lipid catabolism via *PGC1α* and *PPARα*.

Patients and methods: We selected 6 patients with LSM: 2 RR-MADD, 1 carnitine deficiency, 2 NLSD-M, 1 CPT-II deficiency. Muscle immunofluorescence for TFEB and p62 (marker of protein aggregates) and fetal myosin (marker of regeneration) and immunoblot using p62, LC3 antibodies was done.

Results: While in 2 NLSD-M patients there was a co-localized overexpression of p62 and TFEB in some atrophic fibers, some of which were regenerating, in Carnitine and CPT-II deficiency their reaction appeared normal. In regenerating fibers TFEB localized in the cytoplasm (inactive form), whereas in atrophic fibers it localized in the nuclei (active form). Vacuolated and atrophic fibers did not display p62-positive protein aggregates, indicating, together with the LC3-II and p62 immunoblot analysis, that the autophagic flux is still preserved. Furthermore, we studied plasma myo-microRNA of 3 relatives of another NLSD-M family to observe their regulatory role in muscle. Myomicro-RNAs were inversely correlated to residual muscle mass in this NLSD-M family. Mitochondrial enzymes in two subsequent muscle biopsies of the index patient were decreased revealing an essential role of ATGL in mitochondriogenesis.

Conclusion: Nutrition and autophagy are important in RR-MADD and NLSD-M, when there is a progressive wasting of muscle.

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111
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Genetic profiling of Indian patients with glutaric acidemia type I

S. Muntaj[a], T.P. Kruthika-Vinod[a], A.B. Vedamurthy[b]. *[a]Neurochemistry, National Institute of Mental Health & Neurosciences, Bangalore, India; [b]Department of Biotechnology & Microbiology, Karnatak University, Dharwad, India*

Background: Glutaric acidemia type I (GA-I), is an inborn error of metabolism caused due to deficiency of the enzyme Glutaryl-CoA

Dehydrogenase. There are very few studies on the genetic etiology of GA-I from India.
Objective: The objective of this study was to screen Indian patients with GA-I for commonly occurring high and low excretor mutations.
Materials and methods: The study was approved by the institutional Human Ethics Committee. Fifty confirmed GA-I patients from unrelated families were recruited based on clinical, neuroimaging and biochemical profiles. Informed consent was obtained from patients before taking blood spots on the filter paper and screened for mutations, R402W, A421V and A293T (high excretor) and R227P and V400M (low excretor) by RFLP or by direct sequencing of PCR products. Mutations screened by RFLP were further confirmed by sequencing.
Results: Among the patients, 11(22%) were found to have R402W mutation, 7(14%) were homozygous and 5(8%) were heterozygous. One(2%) had F236L and 1(2%) had R313W mutations. Novel mutations, P286S was found in 2(4%), W225X in 1(2%), H403Y in 1(2%), Y295Y in 1(2%) and 1606 G > T at 3' UTR in 1 (2%). Conversely, none of the GA-I patients had A421V, A293T, R227P and V400M mutations. No novel low excretor mutations were found.
Conclusion: From this study, it is evident that R402W and novel P286S mutations were common among GA-I patients. A421V, A293T, R227P and V400M mutations were found to be absent. In conclusion, R402W and P286S are the most prevalent mutations among GA-I patients from India.

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112
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Familial, autosomal-dominant neurodegenerative parkinsonism with cognitive deterioration spanning five generations in a genetically isolated population of South-Eastern Moravia, Czech Republic

K. Mensikova[a], M. Godava[b], P. Kanovsky[a], P. Otruba[a], M. Kaiserova[a], M. Vastik[a], L. Mikulicova[a], T. Bartonikova[a], R. Vrtel[b], R. Vodicka[b], S. Kurcova[a], P. Jugas[c], J. Ovecka[d], L. Sachova[e], F. Dvorsky[f]. [a]*Department of Neurology, Palacky University Olomouc, Olomouc, Czech Republic;* [b]*Department of Medical Genetics and Fetal Medicine, Palacky University Olomouc, Olomouc, Czech Republic;* [c]*Department of Neurology, Neurology Outpatient Clinic, Veseli nad Moravou, Czech Republic;* [d]*General Practitioner, General Practitioner, Lipov, Czech Republic;* [e]*General Practitioner, General Practitioner, Velka nad Velickou - Javornik, Czech Republic;* [f]*General Practitioner, General Practitioner, Velka nad Velickou, Czech Republic*

Abstract
Objective: To obtain more detailed medical history information about the relatives of individuals with confirmed parkinsonism in an isolated region with a rural population in south-eastern Moravia, Czech Republic.
Background: An epidemiological study conducted over four years revealed an increased prevalence of neurodegenerative parkinsonism in a small, isolated region (10 villages, with a combined population of 8664, with approx. 2927 over 50 years of age) of south-eastern Moravia, Czech Republic.
Methods: Detailed genealogical research was performed on the families of all the subjects with confirmed parkinsonism and the pedigrees were compiled; these were further amended on the basis of information obtained through a consecutive door-to-door survey and by means of local municipal and church registers.
Results: In the first stage, three large pedigrees with a familial occurrence of parkinsonism were found; two of them originated in one of the region's villages. In the second stage, these two pedigrees were completed into one large family tree with an apparent autosomal-dominant inheritance pattern of parkinsonism spanning generations from 1840 to the present.
Conclusions: The high prevalence of parkinsonism in the researched area is caused by the familial aggregation of parkinsonism that was found in two large family trees. This familial aggregation of parkinsonism is probably the result of the genetic isolation of the regional population due to the very low migration rate of its inhabitants to neighboring regions in the last two centuries. A detailed genetic and molecular-genetic analysis are currently underway in all probands in whom the parkinsonism symptoms were documented and in all of their blood relatives.
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113
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Fasting blood glucose levels are associated with white matter hyperintensities' burden in older individuals with and without type 2 diabetes

N. Cherbuin[a], W. Wen[b], P.S. Sachdev[b], K.J. Anstey[a]. [a]*Centre for Research on Ageing Health and Wellbeing, Australian National University, Canberra, Australia;* [b]*School of Psychiatry, University of NSW, Sydney, Australia*

Background: The occurrence of white matter hypointensities (WMH) on T2-weighted (FLAIR) MRI scans is widespread in the ageing population and known to be associated with cerebrovascular disease, cardio-metabolic pathology, and increased risk of cognitive decline and dementia. While WMH have been found to be associated with hyperglycaemia in type 2 diabetes (T2D), it is unclear whether fasting blood glucose (FBG) levels in the absence of T2D is associated with higher risk of developing WMH.
Objectives: Investigate the association between FBG and WMH burden in older individuals living in the community.
Material and methods: Participants were 401 individuals (aged 60-66 years, 48.6% female) taking part in a large longitudinal study of ageing. FBG levels and WMH measures were obtained at first assessment. T2D classification was based on self-report or a fasting glucose level > = 7 mmol/l. Associations were tested with multiple regression analyses while controlling for age, sex, education, smoking, and intra-cranial volume. Institutional Review Board approval was granted.
Results: Included participants comprised 276 individuals with glucose in the normal range (<5.6 mmol/l), 86 with elevated FBG but without T2D (5.6-6.9 mmol/l), and 39 with T2D. Results showed that higher FBG was associated with greater WMH burden in the whole sample in the right ($p = 0.02$) but not the left hemisphere and particularly so in the frontal and temporal lobes. Sensitivity analyses indicate that these findings were mostly driven by participants with T2D or impaired FBG levels.
Conclusion: Impaired FBG levels are associated with increased WMH burden in older community-living individuals with or without T2D.

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