EP4244

Cerebral metabolism of glucose in mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

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Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is one of the family of mitochondrial cytopathies. A feature of these diseases is that they are caused by defects in the mitochondrial genome which is inherited purely from mothers. Our aim was to study investigate cerebral metabolism by 2-[18F]fluorodeoxy-d-glucose uptake using PET and cerebrovascular reverse capacity by transcranial Doppler sonography in MELAS. Previous studies on some mitochondrialopathie’s patients revealed abnormal accumulations of mitochondria in endothelium, smooth muscle cells, in blood vessels, different parts of CNS (thalamus, cerebellum) and skeletal muscle. Some investigators suggested a pathogenic role of vascular involvement in the MELAS syndrome and other encephalopathies. The patients were divided into three groups: interictal MELAS (6); progressive external ophthalmoplegia (8); and pure mitochondrial myopathy and neuropathy (10). The results were compared with normal control subjects. The diagnoses were based on clinical phenotype and histopathologic and molecular analysis.

Cerebral glucose uptake was impaired in 6 patients, with and without CNS symptoms, particularly in the occipital and parietal lobes. The vasoreactivity of the small arterioles to acetazolamide did not differ significantly between patients and healthy control subjects or between the different groups of mitochondrial disorders. MELAS does not appear to be a functional disturbance of arterioles leading to ischemic vascular event. The clinical symptoms in MELAS are not the result of a mitochondrial angiopathy but are the consequences of a mitochondrial cytopathy affecting neurons or glia. There is no correlation between the decreased glucose metabolism and the duration of the disease.

Disclosure: Nothing to disclose

EP4245

Cerebellar ataxia with CoQ10 deficiency due to a novel mutation in ADCK3

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Background: Inherited ataxias are a group of heterogeneous neurodegenerative disorders transmitted by either an autosomal dominant or a recessive trait. It has been reported that cerebellar ataxia and coenzyme Q10 (CoQ10) deficiency were associated, and, in some cases, carried ADCK3 gene mutations.

Objective: To report a case of adult onset cerebellar ataxia with a severe muscle CoQ10 deficiency due to a novel homozygous mutation of ADCK3 gene

Case report: We report a 48 year old man that, since he was 20 years old, complained of a mild gait imbalance. Neurological examination revealed ataxic gait, dysarthria, mild bilateral ptosis, dysmetria and dysdiadochokinesia. Brain MRI showed mild cerebellar atrophy. EMG showed slight neurogenic changes. Serum lactate was increased. Muscle biochemistry revealed a severe reduction of complex II + III activities. Fibroblasts evidenced spared capacity and coupling efficiency in the lower range of controls and normal mitochondrial respiratory chain enzymes activities. CoQ10 was severely decreased in skeletal muscle and normal in fibroblasts. Molecular studies revealed a novel homozygous two base deletion (p.504del_CT) in ADCK3 gene causing a premature stop codon in the kinase domain of the protein. The patient started supplementation with 600 mg/day of CoQ10. After a year of treatment, a follow up revealed no clinical improvements.

Conclusions: Molecular diagnosis of cerebellar ataxic syndromes represents a challenge for neurologists. When the most common causes of recessive ataxias have been excluded, CoQ10 level need to be measured in skeletal muscle because its deficiency is potentially treatable.

Disclosure: Nothing to disclose
EP4246

ARCA3 due to ANO10 mutations: delineation and genotype/phenotype correlation study

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Introduction: ANO10 mutations have been reported to cause a novel form of autosomal recessive cerebellar ataxia (ARCA). Our objective was to report 9 ataxic patients carrying 8 novel ANO10 mutations to improve the delineation of this form of ARCA and provide genotype/phenotype correlation.

Methods: Between 2010 and 2013, 186 unrelated index patients were consecutively recruited in 4 tertiary centers for inherited neurodegenerative disorders. Genetic analysis of ANO10 was performed in 44 patients by conventional Sanger sequencing. 142 patients were directly analyzed by a targeted exon-capture strategy coupled with multiplexing and high-throughput sequencing of 57 genes causing ataxia when mutated, including ANO10. Detailed phenotype of patients with ANO10 mutations was investigated and compared to the 12 previously reported cases.

Results: Mean age at onset was 33 (17-43) and disease progression was slow. Cortico-spinal tract signs were frequent including extensor plantar reflexes and/or diffuse tendon reflexes and/or spasticity. No patient of our series had peripheral neuropathy. Brain MRI showed marked cerebellar atrophy. The most frequent mutation, a mononucleotide expansion from a polyA repeat tract (c.132dupA) and causing protein truncation, was never observed in homozygosity. Only two truncating mutations were reported in homozygosity, one of which (c.1150-1151del) was associated with juvenile/adolescent onset and mental retardation while we show that the presence of at least one missense or also in-frame mutation is associated with adult onset and slow progression.

Conclusions: ANO10 defect is responsible for ARCA mainly characterized by cerebellar atrophy and lack of peripheral neuropathy. We therefore suggest naming this entity ARCA3.

Disclosure: Nothing to disclose

EP4247

No excess of loss-of-function variants in COQ2 in pathologically confirmed multiple system atrophy

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Introduction: The etiology of MSA is obscure. The only reported association is with variants in the SNCA gene, and recently, Mitsui et al. reported an association with COQ2 variants in familial and sporadic clinically-diagnosed Japanese patients. The COQ2 paper was based on linkage analysis in MSA families and genome-sequencing which detected homozygous and compound heterozygous COQ2 variants in two families. A yeast complementation assay found decreased growth rates in COQ2 mutants, consistent with the view that the association with disease was caused by loss-of-function.

Methods: In a multicentre collaboration, we collected ~300 neuropathologically proven MSA cases. We sequenced the coding region in the longest transcript of COQ2 in definite Caucasian cases and 262 British controls.

Results and conclusions: We identified a COQ2 nonsense mutation that was present at higher frequency in controls than in MSA (R22Stop, 24 vs 9 alleles, p<0.0024) and two other variants which were also found at higher frequency in controls (rs6818847 and rs6535454). No association between the synonymous COQ2 SNPs rs183012002 and rs1129617 was observed. Four heterozygous rare coding-variants were detected: the p.S57T mutation reported by Mitsui et al. was present in one case and one control, the p.P68S variant was present in one MSA case as was rs121918231, and the rare SNP rs183012002 was identified in 2 MSA cases and 6 controls. These data suggests that loss-of-function of COQ2 variants are not associated with MSA in Caucasians and suggest that the reported association in the Japanese population should be re-evaluated in further populations.

Disclosure: Nothing to disclose
**EP4248**

**Bladder and bowel dysfunction in female carriers of X-linked adrenomyeloneuropathy**


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**Introduction:** Adrenomyeloneuropathy (AMN) is an X-linked disorder caused by mutations of the ABCD1 gene, and characterized by involvement of the spinal cord and peripheral nerves. The aim of this study was to evaluate bladder and bowel symptoms in men with AMN and female carriers.

**Methods:** In this cross-sectional study, AMN patients attending a tertiary care service completed standardized questionnaires for bladder and bowel, i.e. the Urinary Symptom Profile (USP), Qualiveen Short Form (SF-Qualiveen), International Prostate Symptom Score (IPSS) and the neurogenic bowel dysfunction (NBD) questionnaires.

**Results:** 48 patients participated, 19 males (mean EDSS score (n=16) 3.9 (0-8.0)) and 29 females (mean EDSS score (n=25) 3.2 (0-8.0)). Overactive bladder (OAB) symptoms were common in both males (100%, n=19) and females (86.2%, n=25). There was no significant gender difference in severity of OAB symptoms (p=0.35) and impact on quality of life (p=0.13). Furthermore, there was no significant difference in OAB severity when symptoms were compared between female carriers and a cohort of women (n=17) with spinal cord damage due to multiple sclerosis, (p=0.27). 21% (n=4) of males and 10% (n=3) of females had moderate to severe bowel dysfunction.

**Conclusions:** Bladder and bowel complaints are common in AMN and have a significant impact on quality of life, yet are under-recognized and under-treated. Female carriers in this X-linked disorder can experience bladder symptoms as severe as in males, and comparable to bladder symptoms following spinal cord damage from other causes.

**Disclosure:** Dr Tudor is a recipient of EFNS Department - Department Co-operation Programme.

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**EP4249**

**The dystrophin gene and cognition in the cognitively healthy population**


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**Introduction:** Mutations in dystrophin gene (DMD) have been recognized as a cause of the most common form of muscular dystrophy during childhood, Duchenne muscular dystrophy (DMD). The DMD patients have increased risk for intellectual disability and neurocognitive function impairment and a higher incidence of different neuropsychiatric disorders, such as autism spectrum, attention deficit hyperactivity disorder and obsessive-compulsive disorders. The aim: To investigate whether single nucleotide DMD variants associate with variability in cognitive functions in healthy populations.

**Methods:** The study included 2,704 participants from the Erasmus Rucphen family (ERF) and Rotterdam Study (RS) whose exomes were sequenced and who were assessed for various cognitive traits. The association between DMD variants and cognitive ability was determined using linear (mixed) modeling with adjustment for age, sex and education.

**Results:** We found evidence of association of rs147546024 (β=1.786, p-value=2.56*10-4) with block design test in ERF and rs1800273 with block design test in ERF (β=0.424, p-value=0.066) and Mini-mental state examination test in the RS (β=0.465, p-value=0.002). Both variants are highly conserved, although rs147546024 is an intronic variant with unknown effect on the protein, whereas, rs1800273 is a missense variant in the DMD which has a predicted damaging effect on the protein.

**Conclusions:** The analysis of sequence variants in the exon of DMD suggests the existence of variants in the DMD which may effect cognitive functioning in the general populations. Larger studies are required for confirmation.

**Disclosure:** Nothing to disclose
EP4250
Relapsing remitting multiple sclerosis in X-linked Charcot-Marie-Tooth disease with central nervous system involvement
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Introduction: X-linked Charcot-Marie-Tooth disease (CMTX) is a hereditary sensorimotor neuropathy caused by mutations in the GJB1 gene coding for connexin-32 (Cx32). Cx32 is a gap junction protein expressed in peripheral Schwann cells, but also found in oligodendrocytes within the central nervous system (CNS). Subclinical CNS involvement, documented on brain MRI or electrophysiological tests and, less commonly, clinical involvement ranging from extensor plantars to acute transient encephalopathy, can be observed in patients with CMTX. To date, there have been two case reports of patients with CMTX that developed CNS demyelinating disease compatible with the diagnosis of multiple sclerosis (MS).

Case report: We report a patient who developed clinically typical relapsing remitting MS with characteristic MRI findings and also had CMTX, carrying a novel GJB1 mutation affecting Cx32 (c.191G>A, p. Cys64Tyr). This report is unique compared to previous similar cases in that other family members carrying the same mutation were documented as having mild clinical or subclinical CNS involvement, with diffuse white matter hyperintensity on brain MRI.

Conclusions: Although the co-occurrence of MS and CMTX may be a chance association, the increasing number of cases reported, especially with GJB1 mutations appearing to affect the CNS, may imply some causative effect and provide insights into MS pathogenesis.

Disclosure: Nothing to disclose

EP4251
Monogenic ischemic stroke in young adults. A 5-year experience at the Neurological Institute of Pisa, Italy
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Introduction: Ischemic stroke is a complex disorder resulting from the interplay of genetics and environment. In some instances (especially in young adults) stroke is the direct result of a monogenic disease. Ischemic stroke in young adults is a major health problem being associated with increased morbidity and mortality and with a stroke recurrence rate of 25% during the first decade. However, exact epidemiological data are not known. Identifying the cause of ischemic stroke in young adults might be of major importance to prevent stroke recurrence.

Methods: A total of 120 cases (55% women) aged 18 to 55 years who developed a first ischemic stroke were identified in the Cerebrovascular Register of our Institut (2008-2013). After exclusion of 55 patients with identified stroke cause (e.g., cardiologic, thrombophilic and/or immunological conditions), we evaluated the etiology in the remaining 65 cases.

Results: We identified three MELAS cases, two cases of Fabry disease, six CADASIL cases, one pseudoxanthoma elasticum, one hereditary hemorrhagic telangiectasia and one case of Moya-Moya. The percentage of molecular proven genetic stroke in our juvenile population was 10.8% (13/120).

Conclusions: Given the wide variety of potential underlying causes, the diagnostic work-up of stroke in young adults requires a different approach from that in the elderly. Once excluded medical conditions potentially causing stroke, a comprehensive genetic screening should be performed. Despite such a comprehensive work-up, about 80% of cases will remain unexplained, leading to the diagnosis of idiopathic ischemic stroke.

Disclosure: Nothing to disclose
EP4252

Hereditary spastic paraplegias: design of a diagnosis kit using next generation sequencing

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Introduction: Hereditary spastic paraplegias (HSP) are heterogeneous neurological disorders that can be explained by mutations in ~70 genes. Phenotype-genotype correlations exist for few genetic entities but it is often impossible to predict the mutated gene on the basis of clinical grounds which complicates genetic diagnosis in clinical practice.

Methods: We designed a diagnosis kit to sequence 34 HSP genes simultaneously. All coding exons of groups of 12 patients (multiplexing) are captured in two successive assays using ROCHE/NIMBLEGEN probes and then sequenced on the Miseq sequencer (ILLUMINA). The results were analysed using Genomics Workbench (CLC Bio).

Results: Data analysis of 60 patients (including 8 with known genotypes) indicated that 95% of the sequence reads mapped to the targeted human genomic regions, indicating high specificity of the designed probes. <3% of the targeted regions were not captured. 96% of target bases were covered >50x. All known variants were detected and included single nucleotide variations (SNV), insertions, deletions (up to 29pb), and exon inversion.

In patients with unknown genetic status, a mean of 25 variants were identified. Data filtering based on their nature, effects and frequency in public exomes pinpointed 1-3 variants in 50% of the patients, including a duplication, two exon deletions and a large deletion of 3 successive exons that are under validation (Sanger sequencing, cosegregation analysis and CGH).

Conclusion: The combination of targeted exon capture and next generation sequencing is efficient to detect SNV and rearrangements in HSP patients and to reduce cost/time in clinical practice.

Disclosure: Nothing to disclose

EP4253

Effects of polymorphisms of the CXCR5, TNFSF14 and SLC30A7 genes in multiple sclerosis patients in Csongrád County in Hungary and the North-Bácska region in Serbia

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Introduction: Multiple sclerosis (MS), an inflammatory autoimmune disease affecting the central nervous system, is potentially the most common cause of neurological disability in young adults. Genetic factors and environmental impacts have been implicated in the aetiology. The major histocompatibility complex has been reported to be the strongest genetic susceptibility factor, but there are single nucleotide polymorphism (SNP) differences, which may be protective or risk factors. In the present work, three loci have been associated with MS.

Methods: Taqman probes were applied for allele discrimination in the 477 MS (relapsing-remitting or secondary progressive) and age and sex-matched 481 control samples. For data evaluation, SPSS software version 20.0 was used.

Results: Our results indicated the association of the SNP rs630923 (located in the CXCR5 gene) genotype with MS (p=0.029); the protective effect of the A allele was confirmed (p=0.010). Two further genes influenced the age at onset of the disease. The A allele of the TNFSF14 gene rs1077667 polymorphism showed a protective effect (p=0.031), whereas the G allele was a risk factor (p=0.0079). The G allele of the SLC30A7 rs11581062 polymorphism was identified as a risk factor as concerns the age at onset of the disease (p=0.013).

Conclusions: Our results verify the connection of these three newly identified MS risk loci with the disease, and demonstrate for the first time the impact of the SNPs of these two genes on the age at onset of MS.

Disclosure: Nothing to disclose
EP4254

Gene expression profiles in neuro-Behçet’s disease during active and inactive stages

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Introduction: Neuro-Behçet disease (NBD) primarily causes lesions in the brain parenchyma but rarely it can also lead to dural sinus thrombosis (vascular). In individuals with genetic susceptibility, microorganisms as well as several environmental factors are believed to trigger the inflammation attacks.

Methods: To determine gene expression differences in parenchymal and vascular NBD subtypes and uncover genetic factors causing NBD attacks, whole-genome expression profiles were examined in the peripheral blood mononuclear cells of 1 vascular and 3 parenchymal NBD patients during active and inactive stages using gene expression microarray method by Illumina Human HT12 BeadChip. Raw data were analyzed by GenomeStudio Gene Expression Module v1.0. Quantile normalization and log transformation were performed by bioconductor and R-package. Genomic differences between active and inactive stages were calculated by rank product method.

Results: Genes with more than 2-fold expression increase during active stage (with a significance of p≤0.05) were defensin alpha 1, defensin alpha 3, olfactomedin 4 and neutrophil expressed elastase. Both vascular and parenchymal NBD patients displayed a significant increase in the expression of these four genes.

Conclusions: Defensins and elastase are involved in antimicrobial host defense, whereas olfactomedin 4 is an anti-apoptotic factor. All four differentially expressed factors are primarily produced by neutrophils and NK cells emphasizing the significance of these cell subsets in NBD pathogenesis. Vascular and parenchymal NBD patients overexpress identical genes suggesting that anatomical allocation of NBD lesions is regulated by environmental rather than genetic influences. Our studies need to be validated with larger number of patients.

Disclosure: Nothing to disclose

EP4255

Progressive external ophthalmoplegia – a common phenotype of SPG7 in Norway

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Introduction: Spastic paraplegia 7 (SPG7) is an autosomal recessive form of Hereditary Spastic Paraplegia (HSP) caused by mutations in the SPG7 gene, which encodes paraplegin, a member of the AAA family of ATPases, located at the inner mitochondrial membrane. Respiratory chain dysfunction has been reported in muscle in SPG7 patients, but the molecular aetiology of the disease remains unknown. We have previously reported secondary mtDNA damage in SPG7 patients. We report a novel SPG7 mutation in four Norwegian families presenting with a phenotype consistent with mitochondrial disease.

Material and methods: Patients from four Norwegian families with a phenotype of progressive external ophthalmoplegia (PEO) and spastic paraplegia were examined clinically. Of four index patients, Sanger sequencing of the SPG7 gene was done in two, and exome sequencing done in two.

Results: By Sanger sequencing of the SPG7 gene we found a novel SPG7 missense mutation in two families, c.2102A>C, which was homozygous in the first family and compound heterozygous in trans with the known pathogenic mutation c.1454_1462del in the second family. Exome sequencing in two patients from two other families showed compound heterozygous mutations with c.2102A>C and c.1529C>T.

Discussion: We report a novel SPG7 mutation causing a complex HSP phenotype with PEO, a common mitochondrial disease phenotype. Exome sequencing proved to be a good diagnostic method. Our findings confirm that PEO is not an uncommon presentation of this disorder, and we recommend SPG7 gene analyses to be included in the diagnostic workup of autosomal recessive PEO, especially when spasticity is present.

Disclosure: Nothing to disclose