Cognitive and psychiatric aspects of mitochondrial encephalomyopathies

Doctoral thesis

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Introduction

Mitochondria are intracellular organelles with possible common origin to bacteria (endosymbiotic theory). They are the sites ATP (adenosine triphosphate) production via oxidative phosphorylation (OXPHOS) but are also involved in cell-specific functions such as steroid- and amino acid synthesis, neurotransmitter metabolism, intracellular calcium homeostasis and in the regulation of apoptosis. Mitochondria uniquely contain their own double-stranded 16.6 Kb circular genome (mitochondrial DNA, mtDNA) that is separate from nuclear DNA but is in a complex interaction with it [nuclear-mitochondrial intergenomial communication]. MtDNA has only 37 genes; the majority of mitochondrial proteins are encoded by nuclear DNA. Thereby, mutations in either the mtDNA or the nuclear DNA can result in mitochondrial disorder (MTD).

Although prevalence estimations vary widely; mitochondrial dysfunction is probably the most prevalent metabolic abnormality considering the pivotal role mitochondria play in the metabolism. More than 200 genetic causes have been identified as potential causes of MTDs. Because of polyplasmy, heteroplasmy, the threshold effect and the genetic bottleneck effect, all characteristic of the mtDNA, clinical symptomatology vary a lot even within the same family. In cells highly dependent on OXPHOS, low amounts of mutant mtDNA cause dysfunction making the brain, heart and skeletal muscle the most heavily affected organs. Neurons critically depend on mitochondrial function for their metabolism, to establish membrane excitability and to execute the complex processes of neurotransmission and plasticity. Actually, growing pharmacologic, genetic, biochemical and morphological evidence support the involvement in mitochondria in psychiatric and neurodegenerative disorders. Dysfunction of the central nervous system (CNS) can result in the combination of neurologic, psychiatric and neuropsychologic symptoms. However, very few studies have so far been carried out assessing psychiatric or cognitive symptoms in patients with MTD.

Objective

1. As a national tertiary care center, we aimed to comprehensively assess the frequency of the most common mitochondrial mutations in a cohort of 882 Hungarian patients.

2. We aimed to carry out the complex clinical evaluation and assessment of psychiatric symptoms in a well-defined subcohort of patients with genetically proven primary mtDNA mutations as compared to disease controls, harboring the CMT or HNPP type PMP22 mutation, living with similar level of disability.

3. Our goal was to comprehensively assess neuropsychological symptoms in the same cohort and compare the results to those of matched healthy controls.

4. We aimed to raise awareness to mitochondrial disorders in the international medical community with case reports.

5. We put emphasis on the continuation of our biobank- and register building activity (NEPSYBANK, SCHIZOBANK)

Patients and methods

Epidemiological study

A total of 1328 Hungarian patients were tested from the North-East, South-West and Central region of Hungary (Szabolcs-Szatmár-Bereg, Borsod- Abaúj-Zemplén, Hajdú-Bihar, Baranya, Pest counties and Budapest) between January 1999 and December 2012. A subcohort of 882 [485 female, 397 male; 740 adult and 142 children, mean age 38.8±19.1 years (female: 38.3±15.3 years, male 33.4±17.2 years) with a range of 1-75 years] patients were screened for A3243G, A8344G, T8993C, T8993G and mtDNA deletions. Patients were referred from county hospitals to the three genetic centers, based on the symptomatology and laboratory findings, for further evaluation and genetic analysis. All adult patients had a presentation consistent with mitochondrial disease i.e. the various combinations of symptoms such as short stature, epilepsy, ataxia, myopathy, lipomatosis, ophthalmoplegia externa, hypoacusis, exercise intolerance, myalgia, recurrent ischaemic stroke syndrome, cognitive dysfunction, psychiatric or endocrine disorder. In 70% of the investigated cohort, more than 5 organ systems were affected. Leading symptoms were myopathy, exercise intolerance, ataxia, PEO and psychiatric disorders. Patients with advanced age and/or any autoimmune disorder were excluded from the cohort with deletions because of the frequent occurrence of secondary somatic mutations in both case scenarios. In the case of young children, mitochondrial disease was suspected on the bases of muscle hypotonia, delayed psychomotor development, lactic acidosis and epileptic seizures.

We have screened 446 patients [217 male, 229 female, 366 adult and 80 children, 35.82±18.47 (male: 32.58±17.72 years, female: 38.98±18.64) with a range of 7-63 years] for the three primary LHON mutations (G3460G, G177884G, T14484C), based on the suggestive symptomatology. Written, informed consent was obtained from all participants. The study was carried out according to the Helsinki Declaration and was approved by the Research and Ethics committee of Semmelweis University.

Psychiatric and neuropsychologic study

Nineteen patients (Patient 1-19, 13 female, 6 male) with primary mutation of the mtDNA were selected for a detailed psychiatric and neuropsychologic assessment. Of the 19 patient, only 13 probands has been included in the statistical analysis in order to keep the variables independent. Mean age for the 13 probands, included in the statistical analysis was 34±8.43 years (male: 27.25±6.8; female: 36.66±7.65), average years of education was 12.84±1.21 years (male: 13.25±1.5; female: 12.66±1.12). As control for the psychiatric assessment, 10 patients (HN patients, Patient 20-29, 4 female, 6 male, mean age was: 40±10.99, average years of education was 14.2±3.85 years) with PMP22 mutation were examined. Diagnosis was based on clinical features supported by the presence of the PMP22 gene mutation in HN patients. Thirteen healthy controls matched for age, sex and education (9 female, 4 male, mean age: 33.77±9.19, average years of education 14±0.9 years) were examined for the neuropsychological examination. All participants of the study were Caucasian and visited the clinic within 1 year. Written, informed consent was obtained from all participants. These studies were carried out according to the Helsinki Declaration and were approved by the Research and Ethics committee of Semmelweis University.

Methods

Histopathological evaluation was carried out using standard methods. Mitochondrial disorder was supported by the presence of ragged blue, ragged red and COX (cytochrome oxidase) negative fibers.

DNA was extracted from blood (in 570 cases) or if the blood sample yielded no result but the suspicion of MTD was high, skeletal muscle tissue (in 312 cases) by QIAamp DNA Blood or Tissue kit, according to the manufacturer's (QIAgen, Hilden, Germany) instructions. The A3243G, A8344G and T8993C/G mutations were screened based on a method described earlier using restriction fragment length polymorphism (RFLP) after PCR amplification. The entire mtDNA tRNA was sequenced in 200 cases (120 female, mean age: 30.8±11.3, 80 male, mean age: 29.9±13.5) where there was a high suspicion of MTD based on myopathology and/or clinical symptomatology but no common

mutation was found. The ratio of heteroplasmy was measured by Quantity One Software (Bio-Rad Corp. Hertfordshire, UK). The mtDNA deletion was screened for by long PCR methods using Phusion DNA Polymerase (Finnzymes). The PMP22 deletion and duplication in the HN group was detected with real time PCR as published earlier (Aarskog et al, 2000). The 5HTTLPR (serotonin-transporter-linked polymorphic region) genotypes of both MTD and HN patients were detected by previously reported method (Heils et al, 1996).

In the case of the 19 selected patients, functional ability was assessed using the Hungarian validated version of the Stanford Health Assessment Questionnaire 20-item Disability Index (HAQ-DI). Patients' charts were reviewed for duration of disease, medication and brain CT or MRI scans in case of the 19 patients selected for further evaluation. Psychiatric assessment used the Symptom Checklist-90-Revised (SCL-90-R) and the Beck Depression Inventory-Short Form (BDI-SF) self inventories. The clinician-administered 21-item Hamilton Depression Rating Scale (HDRS) and the clinical version of the Structured Clinical Interview for the DSM-IV axis-I (SCID-I) and axis-II disorders (SCID-II) were also used.

Cognitive functions were evaluated by the Rey Auditory-Verbal Learning Test (RAVLT), the Stroop Color (Stroop C) and Color-Word (Stroop CW) tests, the Trail Making Tests (TMTA, TMTB), the category (aka semantic) and letter Fluency Tests and the Hungarian validated version of the Wechsler Adult Intelligence Scale.

The frequency of the mutations was calculated from the number of patients with pathogenic substitutions divided by the total number of investigated patients. The 95% confidence interval (CI) was calculated according to the standard method.

In the other studies, correlation of total scores in GSI, BDI and HDRS with HAQ-DI in both groups was evaluated using Pearson's correlation. Differences between the patient and control groups were assessed using Chi-Square test for categorical variables and parametrical (t-test) or non-parametrical tests (Wilcoxon Mann-Whitney test) for continuous variables (depending on the distribution of the variables). The normality of the data was checked by Shapiro-Wilk test (data not shown). All tests were two tailed and p values ≤ 0.05 were deemed significant. SCL-90-R was analyzed with SAS System for Windows (Release 9.1 TS Level 1 M3, Statistical Analysis System, SAS-Institute USA).

Results

Epidemiology

We performed the first systematic assessment of the frequencies of the most common mtDNA mutations - A3243G, A8344G, T8993C and T8993G tRNA mutations and the common mtDNA deletions - in Central-Eastern Europe. The A3243G substitution in the $tRNA^{Leu1(UUR)}$ was found in a heteroplasmic form in 11 index patients and further 15 family members from the investigated 882 patients. The frequency of the A3243G mutation was 2.61% (95% CI: 0.0207-0.0315). The heteroplasmic A8344G mutation of the mitochondrial $tRNA^{Lys}$ gene was present in 13 patients from 3 families, which is 1.47% (95% CI: 0.0106-0.0187).

With sequence analysis of the tRNA, we found 6 further pathogenic mutations in 17 (11 female, 6 male) patients out of the 200 investigated cases which is 1.93%.These were the T3250C, the G4298A, the A7445G, the T7510C and the new, pathogenic A8332G mutations. The overall frequency of tRNA mutations was found to be 6.35% (56/882 cases) in the Hungarian population.

Of the protein coding mutations, the T8993C and T8993G substitution that were present in 4 cases among 882 patients, yielding an overall frequency of 0.45% (95% CI: 0.00038-0.0086).

The three primary LHON mutations were detected altogether in 80 cases (41 male, 39 female) in homoplasmic form. The A3460G mutation was found in 9 cases (6 male, 3 female). The G11778A mutation was detected in most cases in 66 cases (34 male, 32 female) and the T14484C was found in 5 cases (2 male, 3 female) from the 446 patients. The frequency of the mutations separately: 2.02% of the G3460A (95% CI: 0.0135-0.0269), 14.80% of the A11778G (95% CI: 0.1312-0.1648) and 1.12% of the T14484C (95% CI: 0.0062-0.0162), the summarized frequency of these mutations was 17.94% (95% Cl: 0.1612-0.1976).

Single mtDNA deletions were detected in 132 out of 882 cases representing 14.97% (95% CI: 0.1377-0.1617), multiple deletions were present in 53 cases which is 6.01% of the investigated cohort (95% CI: 0.0521-0.0681).

Psychiatric and neuropsychologic evaluation

Among the 19 patients selected for further evaluation, ten patients had common mutation of mtDNA (4 cases of A3243G, 4 cases of A8344G and one of the A8332G substitutions). Three patients had protein coding mutation; 2 of them had the T8993G and one had the A12770G substitution. Three patient harbored common mtDNA deletion and four had different combination of nonsynchronous mtDNA SNPs (single nucleotide polymorphism).

In the HN group, 9 patients harbored a duplication (Charcot-Marie-Tooth phenotype, CMT), and 1 had a deletion (Hereditary Neuropathy with Liability to Pressure Palsy phenotype, HNPP) in the PMP22 gene.

In the MTD group, 5 patients harbored the long-long (L/L), 10 patients harbored the long/short (L/S) while 4 patient had the short-short (S/S) genotype (Pt 6, 7, 8, 19). In the HN group, 3 patients had the L/L, further 3 patients the L/S, and 4 patients the S/S polymorphism (Pt 22, 23, 27, 28).

The MTD and HN groups did not differ significantly in gender (χ^2=1.9652; p=0.1610), age (t= -1.42; p=0.1711) or education (t= -1.20; p=0.243). Mean HAQ-DI score was 0.82 in the MT (range: 0 - 1.625) and 0.71 in the HN group (range: 0 - 1.625) which did not differ significantly (p=0.6076) implying comparable level of disability of the two groups. Hypoacusis, ataxia, myopathy, neuropathy and exercise intolerance were the most common neurological symptoms in the MTD group. HN patients mostly had distal type paresis and muscle atrophy. Some patients were taking psychiatric drugs at the time of the assessment. Various alterations have been found on neuroimaging studies, the most common was cerebral and/or cerebellar atrophy.

The MTD and HN groups' BDI-SF and HDRS score differed significantly (12.85 vs 4.40, p<0.031, and 15.62 vs 7.30, p<0.043, respectively). Statistical difference was also found in the GSI score (1.44 vs 0.46, p<0.013) and the nine subscales of the SCL-90-R scale. Patients harboring the S/S genotype had lower levels of depression than the rest of the group (BDI average score of 4.5 vs 11.8, see Table 8).

A variety of psychiatric disorders; current diagnosis in 6 (31%), past diagnosis in 8 (42%), lifetime prevalence in 9 MTD cases (47%) were diagnosed with SCID-I. Personality disorder was found in 8 MTD cases representing 42% of the group.

Int he HN group, depression was more prevalent in the subgroup harboring the S/S genotype than the rest of the group (BDI score of 6.75 vs 2.83). In the HN group, 3 patients (30%) had past and current psychiatric diagnosis. Lifetime prevalence was 20% (2 patients) for dysthymia, 10% (1 patient) for major depression, bipolar II, mood disorder due to general medical condition and alcohol abuse (Table 11). No personality disorder was detected.

On the RAVLT, there positive correlation between the number of words retained and the number of trials, which is slightly stronger in the control group ($r=0.603$, $p<0.0001$ for patients vs. $r=0.748$ $p<0.0001$ for controls). We detected significantly impaired short-term (RAVLT1, mean of patients = 5.46 ± 2.1062, mean of controls = 8.0 ± 1.354, $p = 0.0015$) and delayed recall (RAVLT6, mean of patients: 7.15, mean of controls = 12.15, $p = 0.0001$). The number of read words differed significantly on both the Stroop C and the Stroop CW (Stroop C_60 Pt: 65.77±27.7, controls: 87.08±8.36, $p = 0.018$, Stroop CW_60 Pt: 42.77±22.9, Controls: 61±11.68, $p = 0.021$) No difference has been found in the number of errors on either test (Stroop C_error Pts: 0.77 ± 1.16, Controls: 0.75±1.35, $p = 0.97$, Stroop CW_error Pts: 3±3.96, Controls: 1. 08±1.44, $p = 0.127$). Results on TMT show that patients' performance is over the cut-off values for abnormality (Lezak 2004) (TMTA: 96.39 vs. 86 (1st percentile), TMTB: 186.08 vs. 155 (10th percentile). Motor function was found to be impaired, although patients could perform the task without any mistakes – only in a much slower way (TMTA time Pts: 96.39 ± 62.5 msec, controls: 34.15 ± 8.1 msec, $p = 0.0016$). The difference was greater when motor and executive functions were assessed simultaneously a in a more complex task (TMTB time Pts: 186.08 ± 109.3 msec, controls: 64.39 ± 26.8 msec, $p = 0.0007$). Patients with TMTA time exceding 100 sec performed significantly worse on the WAIS Block Design subscale (mean of Pts with a TMTA_time>100 sec: 71.6, mean of Pts with TMTA_time<100 sec: 96.25, $p = 0.0497$).

In both groups, scores were higher for category than for letter fluency (Pts: 48.77 ± 21.8 vs 23 ± 11.9 ($p = 0.0001$), controls 67.77 ± 12 vs 38.8 ± 10.1 ($p = 0.0001$) showing

better performance. Difference of means was not found to be significant between the groups showing a similar pattern in both groups.

General intelligence, assessed with the WAIS, was in a lower zone of the normal range for the Pt group (FSIQ Pts: 95.2 ± 22.8, controls: 123.7 ± 8.6, p = 0.0003, patients' mean is 76.9% of the controls' mean). The difference between the two groups was significant for both the VQ and the PQ, although a greater impairment was detected in the latter component showing primarily nonverbal impairment (VQ Pts: 97.00 ± 15.7, controls: 117.62 ± 9.9, p = 0.0007, patients' mean is 82.5% of the controls), PQ Pts: 94.1 ± 28.8, controls: 127.23 ± 8.3, p = 0.0006, patients' mean is 73.9% of controls).

Significantly lower score on the WAIS Block Design has been found for those with a long TMTA time (greater than 100 sec) (71.6 vs 96.25, p = 0.0497). A significant positive correlation was found between age and StroopC_60 score (r = 0.601, p= 0.029), as well as between age and TMTA time (r = 0.609, p = 0.027). Negative correlation between HAQ-DI FSIQ was also significant (r = -0.594 p = 0.032). Group I. Pts had significantly worse performance than all other patients on the RAVLT5 (p = 0.01) and sum of letter fluency (p = 0.009). Patients with normal neuroimaging findings had a higher mean FSIQ (110 vs 91.33), VQ (103.25 vs 94.22) and PQ (115.75 vs 84.44) than the rest of the group, although these were not significant differences (p-values of 0.246, 0.427, 0.106, respectively). Patients with structural alteration in the cerebellum had significantly lower PQ (68 vs 105, p = 0.042) and greater VQ-PQ difference (22 vs 5, p = 0.029), than the rest of the group. The VQ and FSIQ scores of the same subcohorts did not differ (p = 0.035 and p=0.088, respectively). In case of Patient 16 we had the chance to do a repeat exam 6 months apart which showed the progression of symptoms.

Case presentation

In the topic of the frequently observed lack of concern about the disease process in our MTD patients, in a previous work, we presented the case of Patient 2, a now 50-year-old female in detail. Our case presentation looked to answer whether it was the physicians' unawareness to rare disorders and frustration of not being able to synthesize the results or the patient's belle indifference that resulted in a 40 years delay of the correct diagnosis.

Her symptoms began in childhood and consisted mainly of ataxia, hearing impairment, balance problems, terminal ileitis and dysthymia. She spent 40 years in the healthcare system with diagnoses such as Fahr syndrome, CADASIL, pseudohypoparathyreosis and somatization disorder, the latter significantly reducing her eligibility for incapacity benefit. On assessment in our center she an elevated level of resting serum lactate (4 mmol/l), creatine-kinase (CK, 305 U/l) and lactate dehydrogenase (LDH, 490 U/l) were found. A neurological examination depicted bilateral ptosis, dysarthria, diffusely hypotrophic muscles, latent paresis of the right arm, distal type of hypoesthesia in all limbs, generalized areflexia and marked truncal ataxia. Psychiatric assessment showed subclinical depression, neuropsychological assessment measured a balanced but subnormal profile. The diagnosis of MELAS syndrome was confirmed by myopathological and genetic investigation.

Biobank- and register building activity

NEPSYBANK, a disease-based biobank collecting both phenotypical and environmental data and biological materials such as DNA/RNA, whole blood, plasma, cerebral spinal fluid, muscle / nerve / skin biopsy, brain, and fibroblast. The target of the diseases is presently stroke syndromes, dementias, movement disorders, motoneuron diseases and mitochondrial disorders. NEPSYBANK coordinates the biobanking activities of the neurological and psychiatry departments of the four medical universities in Hungary. Anamnesis, childhood development, family history, medical and neurological status, ECG, electrophysiological records, neuroimaging, laboratory data, pathological records, respiratory chain activities and medication of patients with MTD has been uploaded to the registry.

Another biobank focusing on the neurodevelopmental disease schizophrenia (SCHIZOBANK) has been built between 2009 and 2013. Mitochondrial dysfunction is frequent in schizophrenia and thus this biobank has been a valuable source of our research. Between 2009 and 2013, detailed clinical data and biological samples of 535 patients with schizophrenia have been uploaded to SCHIZOBANK (www.schizobank.hu) by the participating institutions.

Conclusion

1. We carried out the first genetic epidemiologic study systematically investigating the frequency of the most common mtDNA mutations - A3243G, A8344G, T8993C and T8993G tRNA mutations and the common mtDNA deletions - in Central-Eastern Europe. The mutation frequency in Hungarian patients was similar to other Caucasian populations for the hot spot mutations. The marked variability of published prevalence data is possibly due to the difference in selectional criteria and the examined tissue (blood or muscle), making it difficult to compare results. It is important that similar prevalence studies be carried out in different populations in the future in order to accurately assess the importance and impact of mitochondrial diseases and to adequately manage these patients.
2. Using a comprehensive clinical assessment, we demonstrated that psychiatric symptoms, especially mood disorders are more frequently present in patients with MTD compared to HN patients, who live with comparable level of disability. Psychiatric symptoms of these patients do not have a classic course, are frequently treatment resistant, do not correlate with the severity of the somatic symptoms and thereby might be an independent manifestation of the mitochondrial dysfunction.
3. We elucidated hitherto unknown aspects of cognitive decline in a well-defined cohort of patients with MTD. Our results indicate a decreased but balanced intelligence profile with a variety of focal cognitive deficits present in these patients. Cognitive decline is greater than predicted on clinical grounds or neuroimaging and tend to progress, as demonstrated with the case of Patient 16. Mitochondrial disease is a multisystemic process in which neurodegeneration seems to be present irrespective of the mutation type.
4. In order to raise awareness to MTDs in the international medical community, we reported a case of a woman with multisystemic symptoms where the signs of somatoform disorders were present with laboratory abnormalities and a positive family history, and emphasized that in similar cases mitochondrial workup is warranted to avoid misdiagnosis.
5. We established the registry and biobank of mitochondrial disorders (NEPSYBANK) and schizophrenia (SCHIZOBANK).

List of publications

Papers relevant to the dissertation

1. Reményi V, Inczédy-Farkas G, Komlósi K, Gál A, Pentelényi K, Karczagi V, Melegh B, Molnar MJ: Epidemiological study of the most common mitochondrial DNA mutations in Hungary, 2014 Jan 17. (Impact factor: 1.7)

2. Inczedy-Farkas G – Trampush JW, Perczel-Forintos D, Beech D, Andrejkovics M, Varga Z, Remenyi V, Gal A, Bereznai B, Molnar MJ: Mitochondrial DNA Mutations and Cognition: a Case-Series Report. Archives of Clinical Neuropsychology 2014 Jun;29(4):315-21 (Impact factor: 2.0)

3. Inczedy-Farkas G, Remenyi V, Gal A, Varga Z, Balla P, Udvardy-Meszaros A, Bereznai B, Molnar MJ: Psychiatric symptoms of patients with primary mitochondrial DNA disorders. Behav Brain Funct. 2012 Feb 13;8:9. (Impact factor: 2.13)

4. Inczedy-Farkas G, Molnár MJ: Biobanks. Orvoskepzes. 2011 86:(3:3) 289-290.

5. Inczedy-Farkas G, Remenyi V, Meszaros A, Gal A, Blasko Gy, Bereznai B, Molnar MJ: MELAS syndrome mimicking somatoform disorder. Central European Journal of Medicine. 2011 Vol. 6(6); 758-761. (Impact factor: 0.312)

6. Inczedy-Farkas G, Benkovits J, Balogh N, Almos P, Scholtz B, Zahuczky G, Torok Z, Nagy K, Rethelyi J, Makkos Z, Kassai-Farkas A, Egerhazy A, Tuzko J, Janka Z, Bitter I, Nemeth G, Nagy L, Molnár MJ. SCHIZOBANK - The Hungarian national schizophrenia biobank and its role in schizophrenia research and personalized medicine. Orv Hetil. 2010 Aug 29;151(35):1403-8 [Hungarian]

11.3. Presentations and posters relevant to the dissertation

1. Inczedy-Farkas G, Remenyi V, Gal A, Udvardy-Meszaros A, Varga Z, Molnar MJ: Mitochondrial psychiatry: Clinical practice supports the hypothesis. Mitochondria in life, death and disease, 9-13 May 2012, Crete

2. Remenyi V, Inczedy-Farkas G, Spisak S, Bereznai B, Gal A, Molnar MJ: Mitochondrial DNA resequencing in the diagnostics of mitochondrial disorder. 10th Annual Conference of the Hungarian Neurogenetic Society, 2-3rd of December 2011, Budapest, Hungary

3. Remenyi V, Inczedy-Farkas G, Kalmar T, Spisak F, Bereznai B, Gal A, Rasko I, Molnar MJ: The potentials and pitfalls of genetic resequencing in mitochondrial encephalomyopathies. 7th PhD Symposium Young Scientist Association of the Medical University of Vienna, June 15-16th 2011, Vienna, Austria

4. Molnar MJ, Gal A, Reményi V, Bereznai B, Pal Z, Inczedy-Farkas G, Tyynisma H, Suomalainen A: Nuclear-mitochondrial intergenomial miscommunication. 8th Congress of the Hungarian Humangenetic Society, 2-4th September, 2010, Debrecen, Hungary

5. Inczedy-Farkas G, Meszaros A, Andrejkovics M, Gal A, Remenyi V, Molnar MJ: Neuropsychological and psychiatric alterations caused by mutations of the mitochondrial DNA, American Psychiatric Association, 163rd Annual Meeting, 22-26th of May, 2010, New Orleans, LA, USA

6. Inczedy-Farkas G, Gal A, Pentelenyi K, Remenyi V, Balla P, Andrejkovics M, Molnar MJ: Familial depression associated with two novel T8310G and T8311A mtDNA mutations. 9th World Congress of Biological Psychiatry, June 28th - July 2nd, 2009, Paris, France

11.4. Other papers

1. Nyiro G, Inczedy-Farkas G, Remenyi V, Gal A, Pal Z, Molnar MJ: The effect of the CYP 2C19*2 polymorphism on stroke care. Acta Physiol Hung. 2012 Mar 99(1):33-9. (Impact factor: 0.821)

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3. Makkos Z, Fejes L, Inczedy-Farkas G, Kassai-Farkas A, Faludi G, Lazary J: Clinical characteristics of cannabis-induced schizophrenia spectrum disorder Neuropsychopharmacol Hung. 2011 13(3):127-38

4. Makkos Z, Fejes L, Inczedy-Farkas G, Kassai-Farkas A, Faludi G, Lazary J.: Psychopharmacological comparison of schizophrenia spectrum disorder with and without cannabis dependency. Prog Neuropsychopharmacol Biol Psychiatry. 2011 Jan 15;35(1):212-7 (Impact factor: 3.247)

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