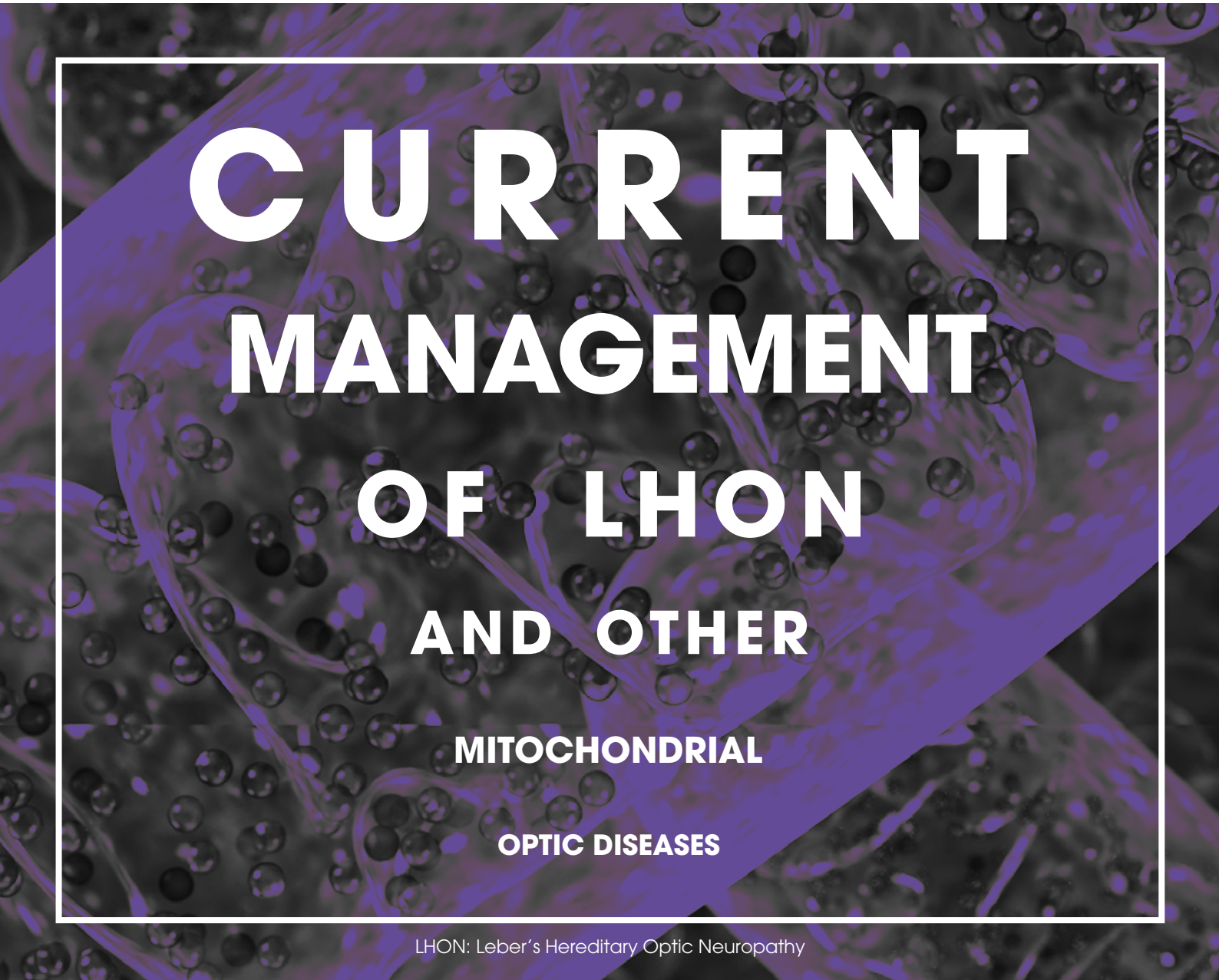
LHON

2nd LHON CEE Expert Forum

6 - 7 December 2017, Grand Hotel Union, Ljubljana, Slovenia

ABSTRACT BOOK



CURRENT MANAGEMENT OF LHON AND OTHER MITOCHONDRIAL OPTIC DISEASES

LHON: Leber's Hereditary Optic Neuropathy

Welcome letter

Dear colleagues and friends,

On behalf of the Neuro-ophthalmological section of the Slovenian Society of Ophthalmology, I wish to express cordial welcome to all who joined this interesting meeting. With the advent of new treatment modalities and development of new OCT, electrophysiological and genetic methods we are rapidly expanding knowledge on the mitochondrial diseases that affect visual system. We regard highly the decision of Ewopharma/Santhera to organise this meeting in Ljubljana as an appreciation of Slovenian neuro-ophthalmology. This event will feature wonderful set of leading international invited speakers and, neuro-ophthalmologists from the region of Central and Eastern Europe. I sincerely hope that our hospitality, culture and nature will keep nice memories of your visit to Slovenia for long.

Marko Hawlina

Day 1

Co-Chairs: Prof. Marko Hawlina and prof. Valerio Carelli

Time	Topic	Speaker
14:00-14:10	Introduction/Welcome notes	Prof. Marko Hawlina
14:10-14:30	Pathophysiology of LHON	Prof. Valerio Carelli
14:30-14:50	Therapeutic strategies for LHON	Prof. Patrick Yu-Wai-Man
14:50-15:10	Idebenone in LHON – new data	Prof. Thomas Klopstock
15:10-15:25	Panel discussion	All
15:25-15:45	*Coffee break*	
15:45-16:05	Diagnostic challenges in mitochondrial optic neuropathies	Prof. Thomas Klopstock
16:05-16:25	OCT in mitochondrial optic neuropathies	Prof. Piero Barboni
16:25-16:45	Role of electrophysiology in the diagnosis of optic neuropathies	Prof. Marko Hawlina
16:45-17:05	Challenges in genetic diagnosis and counselling in LHON patients - a Polish perspective	Prof. Maciej Krawczynski
17:05-17:25	Case presentations	Dr Adrian Burloiu (Romania) Dr Aleks Kree (Estonia) Dr Chiara la Morgia (Italy) Dr Neringa Jurkute (UK)
17:25-17:40	Panel discussion	All
19:30-22:00	*Off site dinner*	

Day 2

Co-Chairs: prof. Thomas Klopstock and prof. Patrick Yu Wai-Man

Time	Topic	Speaker
09:00-09:20	Atypical LHON presentations	Prof. Patrick Yu Wai-Man
09:20-09:40	LHON beyond the eye	Dr Hana Kolarova
09:40-10:00	Mitochondrial diseases in Hungary	Prof. Judit Mária Molnár
10:00-10:20	Clinical findings in patients with OPA1 mutations	Assoc prof Petra Liskova
10:20-10:35	Panel discussion	All
10:35-11:00	*Coffee break*	
11:00-11:20	Mitochondrial diseases and the eye (MELAS, MIDD, CPEO)	Dr Martina Jarc-Vidmar
11:20-11:40	The patient's perspective	Marko Mikulin
11:40-12:00	Case studies	Prof. Sylvia Cherninkova (Bulgaria) Dr Magdalena Korwin (Poland) Dr Tamara Misljenovic (Croatia) Dr Ana Fakin (Slovenia)
12:00-12:20	Panel discussion	All
12:20-12:30	Closing remarks	Prof. Marko Hawlina
12:30-13:30	*Lunch*	

Pathophysiology of Leber's hereditary optic neuropathy (LHON)

Valerio Carelli

Leber's hereditary optic neuropathy (LHON) is the paradigm for mitochondrial optic neuropathies. Outstanding questions on its pathophysiology include:

- the tissue specificity for retinal ganglion cells (RGCs), and even more precisely for those RGCs originating the smallest axons of the papillomacular bundle
- the male prevalence
- the incomplete penetrance
- the subacute catastrophic onset and rapid evolution of LHON natural history
- the spontaneous recovery of visual function in a subgroup of patients.

All these issues have been tackled by intensive research in recent years, which provided some relevant advances in our understanding of LHON. In particular, we reached evidence that efficient activation of mitochondrial biogenesis plays a key role in protecting mutation carriers from developing the optic neuropathy. Gender bias relates to the role of estrogens in activating a successful compensatory increase of mitochondrial biogenesis in females. The efficiency of mitochondrial biogenesis also distinguishes affected of both genders from the unaffected mutation carriers, who on average display the highest mtDNA copy number. The most recent focus is on the counterpart of mitochondrial biogenesis, i.e. mitochondrial quality control and mitophagy. The dissection of the signaling pathways and the genetic background underlying the successful mitochondrial homeostasis will provide key clues on the compensatory mechanisms preserving from blindness in LHON, and will provide new therapeutic targets. Further topics under scrutiny include the role of oligodendrocytes and myelin, the role of astrocytes, and the role of anatomical features such as vascular supply and optic nerve head conformation.

Therapeutic strategies for LHON

Patrick Yu-Wai-Man

Leber's hereditary optic neuropathy (LHON) is an important cause of severe bilateral visual loss among young adults. Patient management remains largely supportive, but major advances in our understanding of the mechanisms underpinning retinal ganglion cell loss in this mitochondrial disorder are paving the way for novel forms of treatment aimed at halting or reversing visual deterioration at different stages of the disease process. This presentation will critically review the evidence base for the various therapeutic strategies that have been put forward to treat LHON and the significant challenges that still lie ahead. LHON causes devastating visual loss and the urgent need to develop and validate new treatments should not cloud our judgement that patient safety should always remain the abiding central factor.

Idebenone in LHON – new data

Thomas Klopstock

Leber's hereditary optic neuropathy (LHON) is caused by mitochondrial DNA mutations that lead to a defect of complex I of the respiratory chain, and subsequently to function loss of retinal ganglion cells and visual impairment. Idebenone is not only a powerful antioxidant but also facilitates electron flux directly to complex III, thus bypassing complex I. Case reports, a retrospective open-label study and a randomised trial (RHODOS) suggested efficacy of idebenone in a subgroup of LHON patients. An Expanded Access Programme to provide idebenone to named patients on an unsolicited basis was set up in 2011. Out of 111 treated patients, 78% (n = 87) had one of the three main mitochondrial mutations, had disease onset < 12 months in the most recent eye and provided baseline and post-baseline measures. Clinically relevant recovery (CRR) of visual acuity (VA) was observed in 47.1% of patients. Analysis of the treatment effect by duration of treatment showed that both the proportion of patients with CRR as well as the magnitude of VA recovery increased with increasing treatment duration. The average gain in visual acuity for responders was 0.72 logMAR, equivalent to more than seven lines on the ETDRS chart after an average treatment of 23.8 months. Furthermore, 50% of patients who had a VA below 1.0 logMAR in at least one eye at initiation of treatment (12/24) experienced a clinically relevant stabilisation (CRS) of vision below this threshold at their last observation. Taken together, these data demonstrate a benefit of idebenone treatment in recovering lost vision and maintaining good residual vision in a real world setting.

Diagnostic challenges in mitochondrial optic neuropathies

Thomas Klopstock

The most frequent inherited optic neuropathies are Leber's hereditary optic neuropathy (LHON) and dominant optic atrophy with OPA1 mutations (DOA-OPA1). In both, mitochondrial dysfunction leads to selective degeneration of retinal ganglion cells (RGCs), particularly in the papillomacular bundle, resulting in temporal pallor of the optic discs and central or coecocentral visual field defects.

Diagnostic challenges include: (i) Awareness of these disorders: this is the prerequisite to initiate the necessary gene tests. (ii) Availability with and access to genetic testing. (iii) Familiarity with which gene tests to request and how to interpret the results; eg, negative results for the three primary LHON mutations do not exclude LHON, sequencing of the complete mitochondrial DNA may be necessary. (iv) Awareness of atypical presentations, eg childhood-onset or late-onset variants of LHON. (v) Awareness of differential diagnoses, including acquired (eg, optic neuritis, toxic opticopathies) and other genetic (eg, DOA-OPA2-8, Wolfram syndrome) forms.

Awareness of these disorders is key to establish the correct diagnosis which is of utmost importance for genetic and life style counselling as well as for therapeutic decisions.

OCT in mitochondrial optic neuropathies

Piero Barboni

The introduction of OCT has changed the approach to mitochondrial hereditary optic neuropathies such as Dominant optic atrophy (DOA) and Leber's hereditary optic neuropathy (LHON).

DOA is characterized by a diffuse thinning of the retinal nerve fiber layer (RNFL), with a preferential involvement of the temporal and inferior sectors corresponding to the papillomacular bundle associated with diffuse macular ganglion cells layer (GCC) reduction.

LHON is characterized by 4 different stages of disease progression: asymptomatic, sub-acute, dynamic and chronic. During each of this stage a specific pattern of RNFL thickening and thinning and GCC thinning can be documented by OCT.

In both diseases, the analysis of optic nerve head (ONH) size is important for prognosis, as a correlation between ONH size and RNFL damage and final visual acuity was found.

Today, the new Swept Source OCT and OCT angiography instruments, allowing the analysis of the choroidal thickness and of the optic nerve head vascularization provided new interesting information, which could elucidate the pathogenesis of the diseases.

Role of electrophysiology in the diagnosis of optic neuropathies

Marko Hawlina

Optic neuropathies are a group of diseases that present with visual loss which can be either unilateral or bilateral, simultaneous or sequential. In initial stages it may be sometimes difficult to diagnose this condition and dissociate it from eventual retinal disease. Electrophysiology is an objctive methodology that can objectively assess retinal and optic nerve function and give information on the level of dysfunction. For this, a battery of tests are used that assess retinal function such as full field ERG in photopic and scotopic conditions, and multifocal ERG (mfERG) that gives topographic functional information of the central part of the outer retina (photoreceptors and bipolar cells). For assessment of ganglion cell function, pattern ERG (PERG) and photopic negative response (phNR) are used. Although elicited mainly by ganglion cells, these responses also contain part of outer retinal activity. Optic nerve function in the clinic is tested by pattern visual evoked potentials that are recorded from the visual cortex. Most often, optic neuropathies can be dissociated from retinopathies by normal retinal responses and abnormal VEP responses.

Sometimes, however, small maculopathies can cause VEP abnormalities and for that purpose, mfERG is most important method to detect macular photorecptor dysfunction.

Optic neuropathies, however, will show normal mfERG responses (provided good fixation can be maintained) in combination with abnormal VEP. Ganglion cell dysfunction may be recorded by abnormal PERG or PhNR. In optic neuropathies, ganglion cell dysfunction may be secondary to optic nerve damage such as in optic neuritis, compressive disorders or glaucoma and therefore PERG or phNR may not be affected in initial stages of the disease as retrograde degeneration of ganglion cells will only occur gradually within weeks.

In LHON, however, the ganglion cell function is primarily affected due to intracellular energy processing damage and therefore, PERG can show early loss of N95 vawe and can therefore serve as an early biomarker of LHON.

As PERG depends on good fixation, phNR (which is a flash evoked response) may offer ganglion cell monitoring, but has been shown to have lower sensitivity than PERG. In conclusion, optic neuropathies may be diagnosed by electrophysiological methods that also offer objective quantification of the damage and show potential for use in follow up studies to objectively monitor the treatment effects. From our research work, primary dysfunction of ganglion cells in LHON shows reduction of N95 amplitude already in early stages of the disease, before the onset of optic nerve palor and can be used as biomarker for LHON.

Challenges in genetic diagnosis and counselling in LHON patients - a Polish perspective

Maciej Krawczynski

Although LHON in known for nearly 150 years it is still a challenge in diagnosis and genetic counselling. First of all, there is still a limited knowledge of this ultra-rare mitochondrial disorder among ophthalmologists and usually the first diagnosis stated in the LHON patients is retrobulbar or intrabulbar neuritis. This causes long but useless treatments and elongation of time necessary to propose the correct clinical suspicion and adequate molecular testing. In my opinion, the crucial factors that can change this situation is to pay much more attention to the maternal family history and to use the mtDNA analysis as a part of routine testing in every young male with any optic neuropathy.

The second problem is based on the complexity of genetics of LHON. Although it is well known that the three main mutations are responsible for approx. 95% of cases, there are also a lot of "private" mutations described in single families. Polish population differs significantly from the data described in the literature. Mutation 14484T>C is stated in extremely small proportion of patients (2 out of 80 LHON families diagnosed in my lab). We also have many patients with mtDNA variants that are really difficult to interpret: a large family with 3635G>A mutation that was finally proved to be pathogenic, single patients with strange variants, such as 3394T>C, 3733G>A, 14501A>G, 14568C>T, 14582A>G, that are not listed or proved to be pathogenic in the MitoMap database and a group of at least 5 patients with typical LHON symptoms and 14498T>G variant usually said to be a neutral polymorphism. Patients with typical LHON symptoms but no typical mutations are generally a diagnostic challenge because they need sequencing of the whole mtDNA that is not a routine service and is not financed by our national health fund.

Another type of challenge is genetic counselling for LHON patients. First of all, even typical mutations show decreased penetrance and we know they are not always a critical pathogenic factor. We observe a few families with two or more brothers, where the younger one is affected and the older ones stays healthy, although they all have the same mutation. The analysis of the level of heteroplasmy is still not done routinely and the possible X-linked locus is still sought for. The situation is even more difficult in the case of females with mutations who are at much smaller risk but the real cause of it is still elusive. The only thing we can do is to inform about the average risk, but we can't individualize it for the patient.

It is especially important for young LHON patients to receive a precise counsel regarding the visual prognosis to choose the future education and profession. We must inform about possible spontaneous remissions (especially in patients with 3460G>A mutation), dangerous environmental factors that can be avoided, availability of idebenone treatment and close perspectives of gene therapy. We also must warn our patients of costly proposals of "stem-cell therapy" with Wharton's gelly mesenchymal cells offered in some exotic countries, that have no proofs of safety and effectiveness.

Atypical LHON presentations

Patrick Yu-Wai-Man

Leber's hereditary optic neuropathy (LHON) predominantly affects young adult men with a peak age of onset in the third decade of life. In the majority of cases, the disease is monosymptomatic with isolated optic nerve involvement. This presentation will draw attention to atypical LHON presentations in children and the link with more disseminated central nervous demyelination in a subgroup of patients.

LHON beyond the eye

Hana Kolářová

Introduction: Generally, eye is the only affected organ in LHON but a small subgroup of patients will develop additional extraocular features. These are found only in patients with symptoms of optic neuropathy. Methods: In our Centre for Patients with Inherited Optic Neuropathies we performed a detailed neuro-ophthalmic investigation of 54 carriers of one the LHON prevalent mutations: m.11778G>A (n=45), m.3460G>A (n=6) and m.14484T>C (n=3). Results: All but 2 out of 20 symptomatic (S) patients were men, manifesting with progressive, painless, binocular vision loss. The remaining 34 mutation carriers were either asymptomatic, i.e. without the visual impairment (A; n=18) or presented with subclinical symptoms of the disease in neuro-ophthalmic examination (SC; n=16). Interestingly, extraocular symptoms were present in eleven mutation carriers, of those 64 % were either S (n=3), A (n=1) and SC (n=3) women. On the contrary, all of the four men with extraocular symptoms were S. In total, seven patients (n S=4, n SC=3): m.11778G>A (n=6) and m.14484T>C (n=1), had clinical myopathy. In four of those (n S=1, n SC=2, n A=1), carrying a m.11778G>A, available muscle specimen showed focal subsarcolemmal accumulation of succinate dehydrogenase product, cytochrome c oxidase negative fibres in up to 5 % and 15 % of muscle fibres, and decreased activity of complexes I-III to 22-39% of controls. Moreover, in two of these (n S=1, n SC=1) patients we also documented moderate sensorineural hearing loss. The occurrence of peripheral neuropathy and tremor was also increased in our group (both n=5). One of the S patients with tremor and m.11778G>A also manifested with other neocerebellar symptoms including dysarthria, ataxia and hypermetropy. The most remarkable feature is the dominance of extraocular symptoms over only slightly affected visual functions in a family with m.11778G>A mutation (n=5/16). Notably, in three patients with myopathy and hearing loss/peripheral neuropathy, visual impairment is completely absent. Neither mitochondrial DNA nor Whole exome sequencing have not proved any other pathogenic mutation in these probands. Conclusion: Due to the high incidence of extraocular symptoms, especially in the Czech LHON female patients, we emphasize the need for their search and management even in subclinical or asymptomatic cases. Extraocular symptoms without the concomitant visual failure may be the only presentation in LHON patients.

Mitochondrial diseases in Hungary

Mária Judit Molnár

Prevalence estimations for mitochondrial disorders still vary widely and only few epidemiologic studies have been carried out so far. The biggest challenge is that mitochondrial disorders may be the result of both the mutation of the mtDNA or nuclear genes responsible for the mitochondrial function.

In the present work we aim to give a comprehensive overview about frequencies of the most common mitochondrial disorders in Hungarian patients. A total of 1600 patients were tested between 1999 and 2017 for mtDNA disorders. Among them, 952 were screened for the m.3243A>G, m.8344A>G, m.8993T>C/G mutations and deletions, 546 for LHON primary mutations. The mutation frequency in our cohort was 2.71% for the m.3243A>G, 1.47% for the m.8344A>G, 17.94% for Leber's Hereditary Optic Neuropathy (m.3460G>A, m.11778G>A, m.14484T>C) and 0.45% for the m.8993T>C/G substitutions. Single mtDNA deletions were detected in 14.97%, while multiple deletions in 6.01% of the cases. mtDNA depletion was present in 16 children.

Among the nuclear mitochondrial genes mutation have been detected in the following genes: *POLG* in 12 families, *SPG7* in 7 families, *MPAN* gene in 7 families, *PKAN* gene in 5 families, in *OPA1* gene in 3 families, in the *PARK 2* gene in 2 families, in the Twinkle, *RRM2B, DARS2, YARS2, SUCLG, DGUOK, AKDH, MGME1, SACS* genes in 1-1 families. In 1 family we identified a new gene, the *MSTO1* in the background of a mitochondrial disease. The *MSTO1* mutation is associated with myopathy, ataxia and symptoms of neurodevelopmental disorders. Pathogenic trinucleotide repeat expansion was detected in the *FRDA* gene in 22 families.

Mitochondrial medicine has an increasing importance. Increasing knowledge of the bioenergetic aspects of human disease has provided new opportunities for diagnosis, therapy, prevention, and in connecting various domains of medicine.

Clinical findings in patients with OPA1 mutations

Petra Lišková

OPA1 mutations are causing autosomal dominant optic atrophy. Once considered as an ocular disease it is now well established that a subset of patients suffers from additional extra-ocular pathology referred to as `Plus` syndrome. The clinical spectrum associated with OPA1 mutations continues to expand and diversify. For example, most recently several cases with compound heterozygous OPA1 mutations manifesting severe neurodegenerative disorders have been described. The presentation will summarize reported OPA1 phenotypes and show clinical data collected in the Czech OPA1 patient population.

Mitochondrial diseases and the eye (MELAS, MIDD, CPEO)

Martina Jarc-Vidmar

Purpose: To report phenotype and investigate retinal function in Slovene patients with MELAS (mitochondrial encephalopathy with lactic acidosis and stroke like episodes) and MIDD (maternally inherited diabetes and deafness) with confirmed mitochondrial DNA A3243G point mutation and in patients with CPEO (chronic progressive external ophthalmoplegia) with pigmentary retinopathy (Kearns-Sayre syndrome).

Methods: 15 years old girl, 39 years old woman with MELAS and her 46 years old brother with MIDD and 20 and 57 years old patients with CPEO with pigmentary retinopathy were tested with visual field, electrophysiology testing(ERG), autofluorescence (AF) imaging and OCT.

Results: 15 years old girl with MELAS was first seen at the age of 8 years after episodes of blurred vision, headaches and loss of consciousness. Visual acuity and Ishihara was normal, she had left hemianopia, VEP was normal. Post infarction injury to the central nervous system (CNS) not in vascular territories was found, pyruvic and lactid acidosis was present. She had additional infarction at the age of 11 years, bilateral visual function worsened dramatically, VEP showed prolonged latencies and changes in shape, at her fundus no specific changes were found. Adult patient with MELAS with macular dystrophy with glucose intolerance and hearing problems was first seen at the age of 39 years. Irregularities were seen on AF imaging and with OCT. Electrophysiology showed macular dysfunction. At the age of 40 years she was hospitalized at neurology clinic due to ischemic stroke in left parietal–occipital region, lactic acidosis was detected. Later she suffered from two additional strokes in right occipital and parietal region, bilateral visual function worsened dramatically, she is hemiparetic. The brother with the same mutation with diabetes and deafness (MIDD) had slight visual problems in his left eye only. Pigmentary mottling was seen in his left fundus, with localised abnormal AF and irregularities seen on OCT. Two patients with poor visual acuity with ophthalmoplegia and heart conduction problems (CPEO) were operated for bilateral ptosis. Fundus showed pigmentary changes with hypoautofluorescent regions with severely abnormal photopic and scotopic ERG responses and atrophy of outer retinal layers showed on OCT.

Conclusion: Both MELAS and MIDD patients can present with visual symptoms due to retinopathies with heterogenous presentations and variable degrees of RPE atrophy and hyperpigmentation. Additionally severe bilateral visual loss due to infarction injury to the CNS not in vascular territories was observed in both MELAS patients. Patients with Kearns-Sayre syndrome present with poor visual acuity due to severe pigmentary changes of the retina with atrophy of outer retinal layers and abnormal ERG.

SPEAKER

Piero Barboni

Currently, professor Barboni is consultant neuro-ophthalmologist at Scientific Institute San Raffaele, University of Milan and at the Department of Neurological Science of Bologna University

He works in private practice at Studio Oculistico d'Azeglio, Bologna, Italy.

Since 1987s he is devoted to study hereditary optic neuropathies, for which he collaborates with several university-based centers (University of Bologna, University of South California, Los Angeles, USA, University of Sao Paulo, Brazil). These projects includes:

Concerted action of European comunities "Prevention of blindness: molecular research and medical care in retinitis pigmentosa" 1990-1993

The international research project on Leber's Hereditary Optic Neuropathy in Brazil, since 2005

Mitochondrial Disease Working Group Member for the National Institute of Neurological Disorders and Stroke (NINDS) Common Data Element (CDE) Project

Since 1990, he is also working in private practice, with specific attention to the anterior segment surgery (including cataract, glaucoma and refractive surgery) and vitreoretinal surgery.

He is a member of the following scientific societies:

American Society of Cataract and Refractive Surgery (ASCRS)

Association for Research in Vision and Ophthalmology (ARVO)

North American Neuro-Ophthamology Society (NANOS)

He has authored more than 100 papers on international peer-reviewed journals and several books.

SPEAKER

Adrian Burloiu

Adrian Burloiu has graduated the Medical University of Bucharest in 1985. He practices ophthalmology since 1994 and focused on pediatric ophthalmology. From 1994 he is working in the outpatient department of N. Malaxa Hospital, Bucharest doing the screening and laser for diabetic retinopathy. In 1996 he started for the first time in Romania the screening for ROP in two nurseries of Bucharest. From 2000 he started to do laser therapy for ROP, for the first time in Romania. His interest for premature babies made him study electrophysiology in premature babies, whom he did the postnatal screening with visual evoking potential (VEP) since 2003. In 2004 he got the PhD in "Diabetic Retinopathy".

The work with his wife Carmen, pediatric neurologist in Bucharest, made him interested in pediatric neuro ophthalmology and made improve his skills in doing visual evoking potential (VEP) for these patients.

Since 2003 he is doing electroretinography (ERG) for retinal diseases.

CO-CHAIR

Valerio Carelli

Since the original discovery of the first mutations affecting mitochondrial DNA in 1988, Professor Valerio Carelli's career has been dedicated to the study of mitochondrial medicine, with particular reference to mitochondrial optic neuropathies.

LHON has been the first topic explored over 25 years, unwrapping the different layers of the pathogenic mechanism; first investigating the Complex I dysfunction due to LHON mutations, then studying the cell biology of LHON through the model of cybrids. The histopathology of LHON was further investigated under the guidance of Professor Alfredo A. Sadun of Los Angeles, CA, USA, and the first genetic mouse model generated by Professor Doug Wallace was phenotyped.

In 2001 Professor Carelli returned to Italy and took over the Laboratory of Neurogenetics in the Department of Neurological Sciences at the University of Bologna, diagnosing mitochondrial patients and building the clinical cohorts of LHON and DOA; work which now continues at the new IRCCS Institute of Neurological Sciences of Bologna, Bellaria Hospital. Currently, molecular and cellular biology research is carried out at the renewed laboratory of neurogenetics, and clinical translational research thanks to the dedicated clinic of neuro-ophthalmology.

Professor Carelli's research group, uniting the basic science and clinical teams, is composed of four PhDs, three lab technicians, and three MDs (two neurologists and one ophthalmologist). This team enjoys extensive collaborations in Italy and abroad, in particular the rest of Europe and the USA.

SPEAKER

Sylvia Cherninkova

Professor Sylvia Cherninkova graduated in medicine from Medical University of Sofia, Bulgaria in 1978. In 1984 she defended her PhD thesis in the field of Neuro-ophthalmology. In 1985 Dr. Sylvia Cherninkova finished her residency in Neurology (first speciality). She became an assistant in Neurology in the Department of Neurology, Medical University, Sofia, Bulgaria. In 1993 she finished her residency in Ophthalmology (second speciality). In 2008 she defended her DMedSci thesis in the field of neuro-ophthalmology and neurogenetics. Since 2000 she has been an Associate Professor in Neurology and in 2010 she became a Professor in Neurology in the Department of Neurology, Medical University, Sofia, Bulgaria. She currently works as a Head of the Department in the Clinic of Neurology, University "Alexandrovska" Hospital, Sofia and in the Medical University, Sofia, Bulgaria. Prof. Cherninkova mentored 6 PhD students.

In 2004 Dr. Sylvia Cherninkova specialized in the field of genetic investigation of the inherited retinal degenerations in the Institute of Ophthalmology and Moorfields Hospital, London, UK, under the supervision of Professor Shomi Bhattacharya. Her research interests are in the field of neuro-ophthalmology and neurogenetics. She participated as a co-author in more than 30 full paper publications in peer-reviewed journals (Brain, Annals of Neurology, American Journal of Human genetics, European Journal of Human genetics, Molecular Vision, Clinical genetics, Journal of Neurology, Ophthalmologica, Pediatric Neurosurgery etc). Prof. Cherninkova is a Co-Chair of the Bulgarian Neuro-ophthalmology and Pediatric Ophthalmology Society. She is involved as a principal investigator in clinical trial on Leber's hereditary optic neuropathy.

SPEAKER

Ana Fakin

Dr. Ana Fakin graduated in medicine at the University of Ljubljana, Slovenia, in 2009. After completing her internship in 2010 she has worked as a young researcher at University Eye Hospital Ljubljana and completed her PhD on genetic and phenotypic characteristics of Usher syndrome in Slovenia under the supervision of Prof. Marko Hawlina in 2013. She has been a resident of Ophthalmology since 2013. During this time, in the years 2014-2016 she has worked as a postdoctoral researcher at University College of London, Institute of Ophthalmology and co-authored papers on ABCA4 genotype-phenotype correlations with Prof. Andrew Webster, Michel Michaelides and Anthony Moore. She has received an Eberhardt Dodt Memorial Award at the ISCEV meeting in 2015 for her work on electrophysiological characteristics of different ACBA4 mutations. Her main interest is genetic eye disease. She is part of a research group at the University Eye Hospital and has co-authored a paper on LHON in Slovenian patients that was published in Documenta Ophthalmologica in 2015.

CO-CHAIR

Marko Hawlina

Marko Hawlina graduated at Medical Faculty of Ljubljana in 1983 and was awarded PhD at St Thomas' Hospital, University of London in 1995 with Professor Hisako Ikeda, working on electrophysiology and melatonin/dopamine interactions in animal models of retinitis pigmentosa and clinical electrophysiology. There, he developed and patented the HK-loop electrode for clinical electrophysiology, recognized by the International Society for Clinical Electrophysiology of Vision (ISCEV). He attended clinical neuroopthalmology with David Spalton, Elizabeth Graham and Gordon Plant.

He returned to Ljubljana Eye Hospital and established clinical services and research projects in the fields of neuroophthalmology and genetic eye diseases, electrophysiology, and recently, stem cell research. With his group, he published over 70 papers in peer reviewed journals and mentored 10 PhD students. He conducted the research on Slovenian patients with LHON with Dr. Martina Jarc Vidmar and suggested that pattern ERG may be an early biomarker for LHON. He was one of the first researchers to publish on autofluorescence imaging in retinal dystrophies and mentored research on various genetic eye diseases in Slovenia such as RP, Usher Syndrome, Best disease, Stargardt disease and others. He has had a number of invited lectures on genetic retinal diseases and optic neuropathies and collaborated with a number of groups in the UK, France and Germany.

Marko Hawlina currently leads neuroophthalmology and electrophysiology service at University Eye Hospital Ljubljana and chair of ophthalmology at Medical Faculty of Ljubljana. He is board member of European Neuroophthalmological Society (EUNOS) and was local organiser of EUNOS and ISCEV symposia in Ljubljana in 2015. He is also immediate past president of Slovenian Society of Ophthalmology and chairman of Education Committee of the SOE.

SPEAKER

Neringa Jurkute

Neringa Jurkute studied medicine from 2003 to 2009 and achieved Medical Doctor (MD) Qualification at Vilnius University (Lithuania). In 2013 she has finished her ophthalmology specialist training and until 1st November 2016 she was working as a general ophthalmologist with a special interest in Neuro-ophthalmology outgoing patients' clinic and private practice in Lithuania. In 2015 she has passed EBO (European Board of Ophthalmology) exam in Paris and gained FEBO title. From 1st of November 2016 she is working as Clinical Research Associate at University College of London with a Honorary Fellowship contract at Moorfields Eye Hospital in London (UK).

Ever since her medical training in Vilnius University she had a great interest in both the clinical and scientific work. Her fascination with neuro-ophthalmology began in her second year of training, when she started her active participation in international neuro-ophthalmology meetings. Afterwards she started to be interested in dealing with complex systemic diseases that have manifestation in the visual system, different disease pathogenesis, visuoperceptual functions in neurodegenerative disorders, where patients experience visual symptoms attributed to pathology of the afferent and efferent visual systems.

Prizes and Distinctions:

2011 EVER listed countries travel grants.

2012 SOE Educational grant. Observership was held at Moorfields Eye Hospital (London, UK)

2013 SOE Educational grant. Observership was held at Ljubljana University Eye Hospital (Ljubljana, Slovenia)

2016 EURETINA grant. Observership was held at St Thomas Hospital (London, UK)

2017 ESHG (European Society of Humans Genetics) grant.

CO-CHAIR

Thomas Klopstock

Professor Thomas Klopstock studied medicine at Ludwig Maximilian University of Munich, Germany, and at Harvard Medical School, Boston, MA, USA, becoming Doctor of Medicine in 1992.

In 1994, he founded the Mitochondrial Disease Unit at the Department of Neurology, Ludwig Maximilian University of Munich. Remaining at this institution, he became a Consultant Neurologist and Associate Professor of Neurology in 2001. In 2007, he was a visiting researcher at Columbia University, New York, NY, USA, returning to Ludwig Maximilian University of Munich to take up the position of Professor of Neurology at the Friedrich-Baur- Institute, Department of Neurology, which he holds today.

His clinical and research interests embrace neurogenetic disorders, with a particular focus on mitochondrial diseases, the role of mitochondrial dysfunction in neurodegeneration, and the treatment of mitochondrial and other neurogenetic disorders. He has ample experience in conducting randomized controlled trials in rare diseases. Professor Klopstock has been an invited speaker at many international meetings, and is an author of more than 220 peer-reviewed publications.

SPEAKER

Hana Kolarova

Dr. Hana Kolarova graduated in General Medicine from the 1st Medical Faculty at Charles University in Prague in 2013. In support of her passionate interest in inherited metabolic disorders she has joined highly specialized Department of Paediatrics, First Faculty of Medicine and General University Hospital at Charles University in Prague, where, at a Metabolic Ward and Department for Sick Neonates and Infants, she has been working since her graduation. In 2013, she also decided to embark on doctoral studies in Biomedical Sciences in Biochemistry and Pathobiochemistry. Dr. Kolarova research project in Laboratory for Study of Mitochondrial Diseases focuses especially on clinical, biochemical and molecular aspects of mitochondrial optic neuropathies. During her postgradual studies she has also actively participated on the characterization of mitochondrial biogenesis within foetal development. Dr. Kolarova received several fundings for projects "Analysis of risk factors for development of Leber hereditary optic neuropathy (LHON)" and "Mitochondrial diseases with ocular involvement – study of risk factors and optimization of diagnosis and management strategy". Hana has actively participated in the molecular-genetic analysis of OPA1 in a series of 44 probands with a diagnosis of bilateral optic atrophy, in the characterization of LHON/MELAS overlap syndrome, and in the study of ocular presentation of fifty Czech m.3243A>G carriers.

Dr. Kolarova and her co-workers managed to establish a National medical care Center for patients with mitochondrial optic neuropathies with regard to optimize the diagnostic, management and therapeutic strategies. With this particular project, Hana was awarded the 1st place of Albert Schweitzer prize in medicine. Her current effort is to provide the information about the extraocular features in LHON with the cooperation with other european reference centres, especially Institut Imagine at Université Paris Descartes-Sorbonne, where she is currently on an educational stay.

SPEAKER

Magdalena Korwin

Magdalena Korwin since 2001 is the Senior Attendant in the Department of Ophthalmology Medical University of Warsaw. She specializes in anterior segment surgery, oculoplastic and orbital surgery. Adidtionally her special interest is Leber Hereditary Optic Neuropathy, Stargards Disease and corneal disorders and glaucoma.

From 2005 to 2009 she is the member of the Board of the Contact Lens Association of the Polish Ophthalmological Society and national coordinator of the CLEER project.

She was awarded twice for the best research project in the „Dry Eye" competition in 2005 and 2006.

In 2012 she won the award for the „Young Ophthalmologist" for research project „Evaluation of the therapeutic silicone hydrogel soft contact lens fitting in AS-OCT imaging in patients treated in the Department of Ophthalmology Medical University in Warsaw".

In 2015 she received award from the President of the Medical University of Warsaw for being a co-author of the paper „Next-generation sequencing of ABCA4: High frequency of complex alleles and novel mutations in patients with retinal dystrophies from Central Europe".

She is the author and co-author of multiple papers in national and international journals and member of the Polish Society of Ophthalmologists, ECLSO, ESCRS, Retinitis Pigmetosa Society.

SPEAKER

Maciej Krawczynski

Professor Maciej Krawczynski received his MD degree from Poznan University of Medical Sciences (PUMS) in 1991. In the same year he started to work in Department of Medical Genetics. In 1997 he gained his PhD in genetic counselling and in 2003 his habilitation in human genetics and ophthalmology. In 1999 he completed his residency in ophthalmology and in 2005 in clinical genetics. In 1999 he founded the Visual System Disorders Genetic Counselling Unit that is still the only academic unit in Poland that focuses on ophthalmogenetics. Since 2006 he is a member of the Bioethics Committee at PUMS.

In 2009 he took up the position of Professor of Human Genetics at PUMS, Department of Medical Genetics and in 2014 the President of Poland nominated him to become a full Professor of Human Genetics and Ophthalmology.

His clinical and research interests embrace genetically determined eye disorders, especially the genetic background of retinal dystrophies, optic nerves neuropathies and aniridia. He teaches genetics the medical students and residents of ophthalmology, as well as ophthalmogenetics - the residents of clinical genetics. He also diagnoses and counsels the ophthalmogenetic patients from whole Poland working for the Center for Medical Genetics GENESIS in Poznan. He is an author of over 100 peer-reviewed publications. He was a member of the board of the Polish Society of Ophthalmology and now is a member of the board of the Polish Society of Human Genetics. Since 2012 he acts as a Vice-Dean of the Medical Faculty at PUMS.

SPEAKER

Aleks Kree

Dr Aleks Kree graduated in medicine from The University of Tartu, Estonia, in 2008. The residency in ophthalmology was in most part conducted in Eye Clinic of Tartu University, but also in East Tallinn Central Hospital Eye Clinic in Estonia and University Eye Hospital in Ljubljana, Slovenia. His residency was completed in 2011 by taking the national and Fellow of European Board of Ophthalmology exams. Since then, he's been working in the Eye Clinic of Tartu University as an ophthalmologist, teaching students and residents alike.

His main fields of work have been medical retina, medical and surgical glaucoma with different new implants, cataract surgery and all kinds of IOL manipulations, also ocular trauma surgery. Genetical diseases have also been on the agenda, but these being quite rare and Estonia's population rather small, it has amounted to smaller portion of everyday's work.

Dr Kree is a Fellow of European Board of Ophthalmology, as well as Estonian Ophthalmologists Society, Estonian Eye Surgeons Association and Estonian national representitve in European Society of Ophthalmology's Young Ophthalmologist's group.

Dr Kree has been involved in clinical trials on glaucoma and Age Related Macular Degeneration. He has held talks and had presentations in different national and international meetings, amongst others about LHON.

SPEAKER

Marko Mikulin

Marko is a student of economy and has ambitions in entrepreneurship, especially in online business, digital currencies, sales and inovative projects on different fields.

In 2011 he became the member of The Electronic Communications Council of the Republic of Slovenia as a representative of disabled organisations. The council is a body charged with providing advice for directing the development of electronic communications and protecting the interests of consumers in the area of electronic communications. They focused on guidelines for different government bodies on the accessability of web pages, accessability of tv content for blind and partially sighted and deaf people and providing amendments to acts to enforce the rights of disabled people.

In 2013 he worked as a consultant and a tester of the user interface of the app and the performance of the navigating system for the blind with the company Comland on the project ALICE.

In 2013 he worked as an PR assistant on the project ACTIV which seeks to strengthen the active involvement of vulnerable social groups into social life and society by providing training focusing on acquiring skills which boost employment potential.

He assisted on the organisation of the biggest movie event in cinema for the blind and partially sighted in Slovenia (3 movies with audio description and the participation of actors and film makers). He was responsible for the invitations of the blind and partially sighted, the audiance in general and gave interviews to reporters.

He worked as an editor of an audio journal for 2 years (Union of the blind and partially sighted of Slovenia) 2013-2015. He was the member of the general assembly of the Union of the Blind and partially sighted of Slovenia (2013-2017). He is the member of Noordung Blockchain hub Slovenia.

SPEAKER

Chiara La Morgia

Dr. Chiara La Morgia received her MD degree at the University of Bologna in 2002 and completed her residency in Neurology in 2008 at the University of Bologna.

She finished her PhD in Sleep Medicine in 2011 at the University of Bologna. Since 2012 she had a research contract at the University of Bologna. From October 5th 2015 she got a research position at the University of Bologna with a project on hereditary optic neuropathies and melanopsin retinal ganglion cells. Since 2008 she established a collaborative research with the Doheny Eye Institute, University of Southern California, now UCLA, Los Angeles (USA) for the study of circadian photoreception in neurodegenerative disorders. From March 2014 to October 2014 she had a clinical fellowship in neurophthalmology at the Doheny Eye Instiute, University of California, Los Angeles, USA.

She is also part of the team at the neurophthalmology clinic, Bellaria Hospital, UOC Clinica Neurologica, IRCCS Istituto delle Scienze Neurologiche di Bologna.

She is involved since 2004 in different research projects on mitochondrial optic neuropathies including international projects and she is responsible for the clinical management of patients with hereditary optic neuropathies at the Bellaria Hospital. Another focus of her research is the study of the melanopsin retinal ganglion cell system in relation to circadian photoreception in different neurodegenerative disorders including mitochondrial optic neuropathies.

Furthermore, she has been involved in clinical trials on Leber's hereditary optic neuropathy.

She is the PI of a recently funded (by the Italian Ministry of Health) project titled "Melanopsin retinal ganglion cells and circadian rhythms: function and dysfunction in Alzheimer's disease and aging".

She is author of 56 papers in peer-reviewed journals.

SPEAKER

Petra Lišková

A/Prof Petra Lišková studied medicine at Charles University in Prague. She has specialized in ophthalmology and in parallel started researching inherited ocular disorders. She completed her PhD in 2008 at Charles University in Prague. She also undertook postgraduate study at the UCL Institute of Ophthalmology and Moorfields Eye Hospital obtaining Medical Doctor degree (Clinical Research) from University College London in 2009. In 2015 she was promoted to Associated Professor in Medical Genetics and Biology at the First Faculty of Medicine, Charles University.

She is a co-founder of the only specialized ocular genetic clinic within the Czech Republic where she works as a consultant. She is also a representative of the Department of Ophthalmology, First Faculty of Medicine and General University Hospital in Prague within the European Reference Network dealing with rare ocular disorders ERN-EYE.

Petra Lišková has a long-standing experience in ophthalmic genetics with special focus on research and activities related to mitochondrial optic neuropathies and anterior segment disorders. Her research findings include for example the identification and characterization of a novel genetic cause of posterior polymorphous corneal dystrophy.

A/Prof Petra Lišková currently leads her own research group within the Research Unit for Rare Diseases, at the Department of Pediatrics and Adolescent Medicine, First Faculty of Medicine and General University Hospital in Prague. At the UCL Institute of Ophthalmology she holds an Honorary Research Associate position.

Since 2014 Petra Lišková has been acting as the Section Programme Secretary of Molecular Biology/Genetics/Epidemiology at the European Association for Vision and Eye Research.

Clinical work of A/Professor Petra Lišková involves taking care of patients with inherited optic neuropathies as a part of a multidisciplinary team in the General University Hospital in Prague.

SPEAKER

Tamara Mišljenović-Vučerić

Employed at Ophthalmology Department; Clinical Hospital Center Rijeka, Croatia; as head of subspeciality clinics: neuroophthalmology and oculoplastics.

She graduated medicine at the University of Rijeka in 2001 and right after completing her internship in 2002 she started volunteering at Policlinic for Ophthalmology "Dr. Luciana Pavičević", Rijeka. In 2009 she completed her residency in ophthalmology at Clinical Hospital Center Rijeka.

During her residency and as young ophthalmologist she got three grants: one month observership in Moorfields Eye Hospital, London, UK (Adnexal service and External disease and corneal service) and University Eye Hospital, Ljubljana, Slovenia (oculoplastics); and attended one week Ophthalmology seminar in Salzburg, Austria, organized by The American Austrian Foundation.

From 2015 to 2017 she conducted a sub specialization in neuroophthalmology under the supervision of Prof. Branimir Cerovski at Ophthalmology Department of University Hospital Centre Zagreb, Croatia.

SPEAKER

Mária Judit Molnár

Maria Judit Molnar MD, PhD, Professor of Neurology, Psychiatry, Clinical Genetics, and Clinico-pharmacology, Doctor of the Hungarian Academy of Sciences is the director of Semmelweis University's Institute of Genomic Medicine and Rare Disorders, among others president of the Hungarian Medical College of Clinical Genetics, past president of the Hungarian Society of Clinical Neurogenetics, secretary of the Hungarian Society of Personalized Medicine, elected president of the Hungarian Society of Human Genetics, board member of the Neurogenetic and Neuromuscular Committee of the European Academy of Neurology. She was the vice-rector for Scientific Affairs at Semmelweis University (Budapest, Hungary) between 2012 and 2015, where she was also responsible for International Affairs. She has been adjunct professor at the Montreal Neurological Institute, McGill University, between 1999 -2012. Dr. Molnar is the Facilitator of a Challenge Group of the International Consortia of Personalized Medicine initiated by the European Commission. She is the member of the steering committee of the Association of Academic Health Centers International.

Dr. Molnar is recognized as a leading experts on the diagnosis and treatment of rare neurological especially mitochondrial disorders. The Institute of Genomic Medicine and Rare Disorders lead by her offers a comprehensive state of the art, patient-centered care for patients with rare neurological disorders including genetic testing, neuropathological investigations and genetic counselling as well. Dr. Molnar's research covers a broad range of basic and clinical studies on rare neurological disorders, utilizing a broad spectrum of technologies including clinical science, myopathology, molecular genetics including next generation sequencing as well. The Institute of Genomic Medicine and Rare Disorders is the part of the European Reference Network of Rare Neurological Disorders (ERN-RND) and Neuromuscular Disorders (ERN-NMD). Dr. Molnar is the member of the management board of the ERN-RND as the workpackage leader for Education and capacity building.

She plays important role in the organization of rare disease management in Hungary and acts as an ambassador promoting the personalized healthcare. She was the principal investigator of 7 clinical trials, published 1 book, 20 book chapters, 135 papers with cumulative impact factors 176, Hirsch index: 19 and more than 1300 citations. She owns 2 patents.

CO-CHAIR

Patrick Yu-Wai-Man

Affiliations

1. Cambridge Centre for Brain Repair, Department of Clinical Neurosciences, and MRC Mitochondrial Biology Unit, University of Cambridge
2. Cambridge Eye Unit, Addenbrooke's Hospital, Cambridge University Hospitals
3. Newcastle Eye Centre, Royal Victoria Infirmary, Newcastle upon Tyne.
4. Moorfields Eye Hospital and UCL Institute of Ophthalmology, London

E-mail: py237@cam.ac.uk

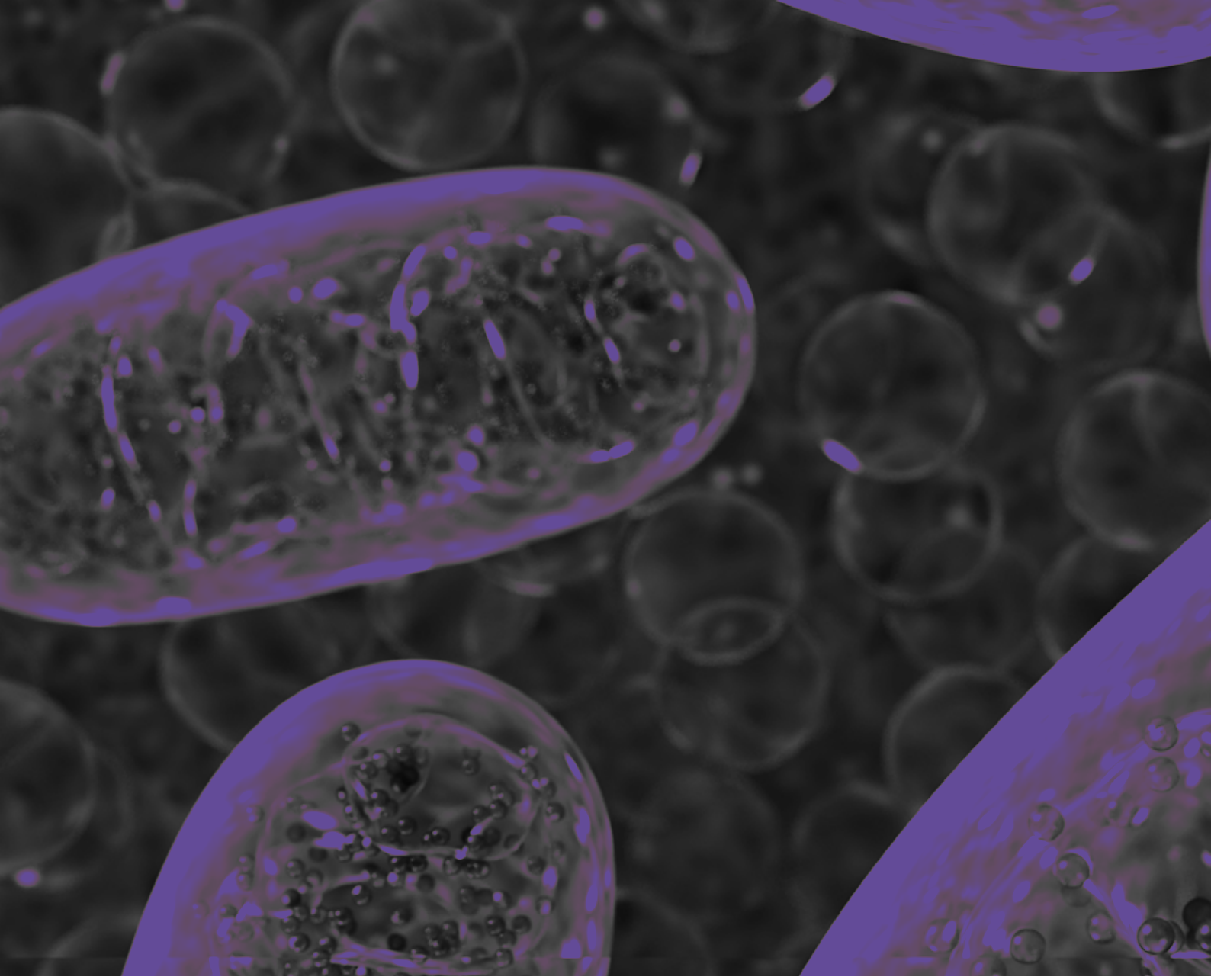
Professor Yu-Wai-Man is an academic neuro-ophthalmologist with a major research interest in mitochondrial genetics and inherited eye diseases. His research programme is currently focused on dissecting the disease mechanisms leading to progressive retinal ganglion cell loss in mitochondrial optic neuropathies by using diseased patient tissues and animal models, in addition to therapeutic drug screening and clinical trials. Through his affiliations in Cambridge, Newcastle and London, Professor Yu-Wai-Man has built a national referral network for the investigation and management of patients with mitochondrial eye diseases. He is actively collaborating with an international network of academic and industrial partners in an effort to fast track the development of effective therapies for this group patients, including novel gene therapy approaches. Professor Yu-Wai-Man is a Council member of the European Neuro-Ophthalmological Society (EUNOS) and he sits on a number of national and international committees (NANOS, JNO, ARVO, EVER).

Notes

Notes

Notes

Notes



A Central and Eastern European Expert Forum supported by Santhera Pharmaceuticals and Ewopharma AG

santhera Pharmaceuticals

ewopharma