

Contents

History of Leber's Hereditary Optic Neuropathy (LHON)	11
1.1. First descriptions and definition of the disorder	11
1.2. Subsequent reports	12
1.3. Genetics	12
1.4. Environment	13
1.5. Treatment	14
1.6. A glimpse into the future	14
Genetics of LHON	18
2.1. Maternally inherited LHON and the role of mitochondrial DNA (mtDNA) pathogenic variants and haplotypes	18
2.2. The new landscape of autosomal recessive LHON (arLHON)	20
2.3. Interacting genetic variants in both mtDNA and nuclear genomes: the digenic model	20
2.4. Questions that remain to be conclusively resolved	21
Epidemiology	28
3.1. Dependence on age and gender	28
3.2. Penetrance and prevalence	28
3.3. Genetic variation	30
3.4. Association with other diseases	30
Molecular background and pathophysiology of LHON	33
4.1. From mtDNA mutations to complex I dysfunction	33
4.2. Complex I dysfunction impacts cell physiology of retinal ganglion cells	34
4.3. The specific vulnerability of RGCs and their axons	35
Phenotypes of LHON	39
5.1. Clinical course of adult-onset LHON	39
5.1.1. Asymptomatic LHON	40
5.1.2. Subacute stage of LHON	41
5.1.3. Dynamic stage of LHON	41
5.1.4. Chronic stage of LHON	41
5.2. Atypical LHON	42
5.2.1. Childhood onset LHON	42
5.2.2. Late-onset LHON	43
5.2.3. LHON plus and LHON-overlap syndromes	43
5.2.4. Atypical clinical course	43
Natural history of LHON	45
6.1. Conversion	45
6.2. Natural history of chronic LHON	45
6.3. Spontaneous visual recovery	49
6.4. Longterm sequelae	54
6.5. Challenges	54

	Diagnostic pathway and differential diagnosis in LHON	56
7.1.	Symptoms and signs	56
7.1.1.	Visual acuity loss	56
7.1.2.	Visual field defect	56
7.1.3.	Fundus exam findings: optic disc hyperemia, microangiopathy and pseudoedema	56
7.2.	Diagnostic pathway: psychophysical findings, electrophysiological testing and retinal imaging	58
7.2.1.	Background	58
7.2.2.	Dyschromatopsia	58
7.2.3.	Pupillary light reflex and pupillometry	59
7.2.4.	Electrophysiological findings	59
7.2.4.1.	Pattern visual evoked potentials	59
7.2.4.2.	Pattern electroretinogram	60
7.2.4.3.	PhNR	60
7.2.5.	Retinal imaging	60
7.2.5.1.	Optical coherence tomography	60
7.2.6.	Optic disc perfusion – laser speckle flowgraphy (LSFG)	62
7.3.	Differential diagnosis of LHON	62
7.3.1.	Optic neuritis (ON) and other inflammatory disorders of the optic nerve	62
7.3.2.	Toxic and nutritional optic neuropathies	62
7.3.3.	Ischemic optic neuropathies	63
7.3.4.	Compressive optic neuropathies	64
	Special topic: autosomal recessive LHON (arLHON)	67
8.1.	<i>DNAJC30</i> -associated LHON	67
8.1.1.	Genetics	67
8.1.2.	Clinical phenotype	68
8.2.	<i>NDUFS2</i> -associated LHON	70
8.2.1.	Genetics	70
8.2.2.	Clinical phenotype	70
	Treatment rationale and approaches	71
9.1.	Natural history and disease staging	71
9.2.	Treatment rationale and therapeutic approaches	72
9.3.	Therapeutic window and current treatments	72
	Idebenone treatment in LHON	76
10.1.	What is idebenone?	76
10.2.	Why idebenone is predestined to work in LHON	76
10.3.	Preclinical studies	76
10.4.	Clinical studies	77
10.5.	Safety and efficacy of idebenone in LHON patients	78
10.6.	Treatment effects in chronic LHON	78

	Gene therapy	80
11.1.	Overview of gene therapy.....	80
11.2.	Development of gene therapy in LHON – Allotopic expression	80
11.3.	Clinical trials of gene therapy in LHON.....	82
11.4.	Gene therapy – Looking to the future.....	84
	Index	87