

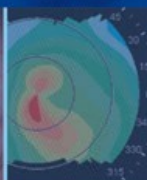
# ESSENTIALS IN OPHTHALMOLOGY

G. K. KRIEGLSTEIN · R. N. WEINREB

Series Editors



Glaucoma



Cataract  
and Refractive  
Surgery



Uveitis  
and  
Immunological  
Disorders



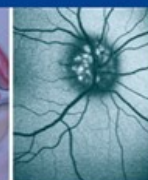
Vitreo-retinal  
Surgery



Medical  
Retina



Oculoplastics  
and Orbit



Pediatric  
Ophthalmology,  
Neuro-  
Ophthalmology,  
Genetics



Cornea  
and External  
Eye Disease

# Pediatric Ophthalmology, Neuro- Ophthalmology, Genetics

Edited by

B. LORENZ

F.-X. BORRUAT

 Springer



Essentials in Ophthalmology

**Pediatric Ophthalmology,  
Neuro-Ophthalmology, Genetics**

B. Lorenz F.-X. Borruat  
Editors



## **Essentials in Ophthalmology**

G. K. Krieglstein R. N. Weinreb  
Series Editors

## **Glaucoma**

**Cataract and Refractive Surgery**

**Uveitis and Immunological Disorders**

**Vitreo-retinal Surgery**

**Medical Retina**

**Oculoplastics and Orbit**

**Pediatric Ophthalmology,  
Neuro-Ophthalmology, Genetics**

**Cornea and External Eye Disease**

Editors Birgit Lorenz  
François-Xavier Borruat

# **Pediatric Ophthalmology, Neuro- Ophthalmology, Genetics**

With 200 Figures, Mostly in Colour  
and 26 Tables

 Springer

## Series Editors

### **Günter K. Kriegelstein, MD**

Professor and Chairman  
Department of Ophthalmology  
University of Cologne  
Kerpener Straße 62  
50924 Cologne  
Germany

### **Robert N. Weinreb, MD**

Professor and Director  
Hamilton Glaucoma Center  
Department of Ophthalmology  
University of California at San Diego  
9500 Gilman Drive  
La Jolla, CA 92093-0946  
USA

## Volume Editors

### **Birgit Lorenz, MD, FEBO**

Professor and Chairman  
Department of Ophthalmology  
Universitätsklinikum Giessen and Marburg GmbH  
Giessen Campus  
Friedrichstraße 18  
35392 Gießen  
Germany

### **François-Xavier Borruat, MD, PD, MER**

Médecin-Adjoint  
Neuro-Ophthalmology  
Hôpital Ophtalmique Jules Gonin  
Avenue de France 15  
CH-1004 Lausanne  
Switzerland

ISBN 978-3-540-33678-5  
Springer Berlin Heidelberg NewYork

ISSN 1612-3212

Library of Congress Control Number: 2007936032

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other way, and storage in data banks. Duplication of this publication or parts thereof is permitted only under the provisions of the German Copyright Law of September 9, 1965, in its current version, and permission for use must always be obtained from Springer. Violations are liable to prosecution under the German Copyright Law.

Springer is a part of Springer Science + Business Media

springer.com

© Springer-Verlag Berlin Heidelberg 2008

The use of general descriptive names, registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

Product liability: The publishers cannot guarantee the accuracy of any information about dosage and application contained in this book. In every individual case the user must check such information by consulting the relevant literature.

Editor: Marion Philipp, Heidelberg, Germany

Desk Editor: Martina Himberger, Heidelberg, Germany

Production: LE-TeX Jelonek, Schmidt & Vöckler GbR,  
Leipzig, Germany

Cover Design: WMXDesign GmbH, Heidelberg,  
Germany

Printed on acid-free paper  
24/3180Wa 5 4 3 2 1 0

# Foreword

The series *Essentials in Ophthalmology* was initiated two years ago to expedite the timely transfer of new information in vision science and evidence-based medicine into clinical practice. We thought that this prosipient idea would be moved and guided by a resolute commitment to excellence. It is reasonable to now update our readers with what has been achieved.

The immediate goal was to transfer information through a high quality quarterly publication in which ophthalmology would be represented by eight subspecialties. In this regard, each issue has had a subspecialty theme and has been overseen by two internationally recognized volume editors, who in turn have invited a bevy of experts

to discuss clinically relevant and appropriate topics. Summaries of clinically relevant information have been provided throughout each chapter.

Each subspecialty area now has been covered once, and the response to the first eight volumes in the series has been enthusiastically positive. With the start of the second cycle of subspecialty coverage, the dissemination of practical information will be continued as we learn more about the emerging advances in various ophthalmic subspecialties that can be applied to obtain the best possible care of our patients. Moreover, we will continue to highlight clinically relevant information and maintain our commitment to excellence.

**G. K. Krieglstein**

**R. N. Weinreb**

Series Editors

# Preface

Neuroophthalmology is one of the most interdisciplinary domains of ophthalmology. It encompasses disorders of both the afferent and efferent pathways whose etiologies may be genetic or acquired, e.g., metabolic, vascular, inflammatory, infectious, tumoral or paraneoplastic. The aim of this monograph is to present the most modern concepts for diagnosing and treating some of these disorders.

We selected topics of particular interest due to the advent of recent diagnostic or therapeutic advances but this list is by no means exhaustive: textbooks in neuroophthalmology usually consist of several volumes! In line with the focus of this series of monographs we have included chapters of immediate clinical relevance as well as science-oriented chapters in order to also provide the reader with some insight into basic research areas that eventually will have an impact on clinical neuroophthalmology.

The volume is organised in six sections: optic nerve; investigations; retinal disorders; systemic diseases; oculomotility; and rehabilitation.

Part I, Optic nerve, discusses optic neuritis and multiple sclerosis, ischemic neuropathies, optic disc drusen, autosomal-dominant optic neuropathy, Leber hereditary optic neuropathy (LHON), optic nerve tumors, and traumatic optic neuropathy including treatment recommendations and experimental data on neuroprotection.

Part II, Investigations, describes and critically evaluates the most recent methods of imaging and electrophysiology of the optic nerve and the central visual pathways.

Part III, Retinal disorders, provides an overview on autoimmune retinopathies and on the basic aspects of cell death as well as on actual and future issues of cell protection and cell rescue.

Part IV, Systemic diseases, covers various aspects of infectious diseases from the retina to the brain, including differential diagnosis and treatment and the latest recommendations in diagnosis and management of giant cell arteritis.

Part V, Oculomotility, covers the cerebral control of eye movements, mitochondrial diseases causing ocular myopathy, and therapeutic options for specific types of neurological nystagmus.

Finally, Part VI, Rehabilitation, summarizes the potentials and limitations of visual rehabilitation in neuroophthalmological disorders.

All chapters are written by leading authorities in their field. We are grateful to the authors for their excellent contributions and also to the publishers for their encouragement and support.

**Birgit Lorenz**

**François-Xavier Borruat**

# Contents

## Part I Optic Nerve

### Chapter 1

#### Optic Neuritis and Multiple Sclerosis

Edward J. Atkins, Valérie Biousse,  
Nancy J. Newman

|       |   |    |
|-------|---|----|
| 1.1   | Idiopathic Optic Neuritis   | 4  |
| 1.1.1 | Clinically Isolated Syndrome  | 4  |
| 1.1.2 | Clinical Features of Acute Idiopathic Optic Neuritis                      | 4  |
| 1.1.3 | Examination Findings in Acute Idiopathic Optic Neuritis                   | 4  |
| 1.2   | Natural History of Acute Idiopathic Optic Neuritis                        | 4  |
| 1.2.1 | Important Studies   | 4  |
| 1.2.2 | Visual Prognosis  | 5  |
| 1.2.3 | Risk of Recurrence of Optic Neuritis                                      | 5  |
| 1.2.4 | Risk of Developing Multiple Sclerosis                                     | 5  |
| 1.2.5 | Severity of Multiple Sclerosis in Patients Presenting with Optic Neuritis | 10 |
| 1.3   | Management of Acute Idiopathic Optic Neuritis                             | 10 |
| 1.3.1 | Diagnosis   | 11 |
| 1.3.2 | Acute Therapeutic Options   | 12 |
| 1.3.3 | Chronic Therapeutic Options   | 13 |
| 1.4   | Pediatric Optic Neuritis  | 14 |

### Chapter 2

#### Ischemic Optic Neuropathies

Anthony C. Arnold

|       |  |    |
|-------|--|----|
| 2.1   | Introduction                                 | 19 |
| 2.2   | Anterior Ischemic Optic Neuropathy           | 20 |
| 2.2.1 | Arteritic Anterior Ischemic Optic Neuropathy | 20 |

|         |   |    |
|---------|---|----|
| 2.2.1.1 | Clinical Presentation                                   | 20 |
| 2.2.1.2 | Pathophysiology   | 22 |
| 2.2.1.3 | Differential Diagnosis                                  | 23 |
| 2.2.1.4 | Clinical Course   | 23 |
| 2.2.1.5 | Diagnostic Confirmation                                 | 23 |
| 2.2.1.6 | Therapy   | 24 |
| 2.2.2   | Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) | 25 |
| 2.2.2.1 | Clinical Presentation                                   | 25 |
| 2.2.2.2 | Pathophysiology   | 26 |
| 2.2.2.3 | Risk Factors  | 27 |
| 2.2.2.4 | Medications   | 29 |
| 2.2.2.5 | Clinical Course   | 30 |
| 2.2.2.6 | Differential Diagnosis                                  | 30 |
| 2.2.2.7 | Therapy   | 31 |
| 2.2.2.8 | Prevention  | 31 |
| 2.3     | Posterior Ischemic Optic Neuropathy                     | 32 |

### Chapter 3

#### Optic Disc Drusen

François-Xavier Borruat

|       |  |    |
|-------|--|----|
| 3.1   | Introduction                                 | 37 |
| 3.2   | Epidemiology                                 | 37 |
| 3.3   | Pathology                                    | 38 |
| 3.4   | Optic Canal Size                             | 39 |
| 3.5   | Associations                                 | 40 |
| 3.5.1 | Inherited Retinal Degenerations              | 40 |
| 3.5.2 | Angioid Streaks and Pseudoxanthoma Elasticum | 40 |
| 3.5.3 | Miscellaneous                                | 40 |
| 3.6   | Paraclinical Investigations                  | 41 |
| 3.6.1 | B-Scan Ultrasound                            | 41 |
| 3.6.2 | Scanning Laser Ophthalmoscope                | 41 |
| 3.6.3 | Optical Coherence Tomography                 | 43 |
| 3.6.4 | Scanning Laser Polarimetry                   | 44 |
| 3.6.5 | Electrophysiology                            | 44 |



|       |  |    |
|-------|--|----|
| 3.6.6 | Retinal Angiography                        | 44 |
| 3.7   | Complications                              | 44 |
| 3.7.1 | Visual Field Defects                       | 44 |
| 3.7.2 | Retinal Vascular Complications             | 46 |
| 3.7.3 | Peripapillary Choroidal Neovascularization | 46 |
| 3.7.4 | Anterior Ischemic Optic Neuropathy         | 46 |
| 3.8   | Therapy                                    | 46 |

## Chapter 4

### Inherited Optic Neuropathies

Marcela Votruba

|         |   |    |
|---------|---|----|
| 4.1     | Introduction  | 51 |
| 4.2     | Primary Inherited Optic Neuropathies with Ocular Manifestations   | 52 |
| 4.2.1   | Autosomal-Dominant Optic Atrophy                                  | 52 |
| 4.2.1.1 | Clinical Features   | 52 |
| 4.2.1.2 | Electrophysiology   | 55 |
| 4.2.1.3 | Histopathology  | 55 |
| 4.2.1.4 | Molecular Genetics and the Genetic Heterogeneity of ADOA          | 55 |
| 4.2.1.5 | OPA4 Locus  | 58 |
| 4.2.1.6 | OPA3 Locus: Autosomal-Dominant Optic Atrophy and Cataract (ADOAC) | 58 |
| 4.2.2   | Recessive Optic Atrophy   | 58 |
| 4.2.2.1 | Clinical Features   | 58 |
| 4.2.2.2 | OPA5 Locus  | 59 |
| 4.2.3   | X-Linked Optic Atrophy  | 59 |
| 4.2.3.1 | Clinical Features   | 59 |
| 4.2.3.2 | OPA2 Locus  | 59 |
| 4.2.4   | Mitochondrial Disease: Leber's Hereditary Optic Neuropathy        | 59 |
| 4.2.4.1 | Clinical Features   | 59 |
| 4.2.4.2 | Findings in Unaffected Relatives                                  | 60 |
| 4.2.4.3 | Systemic Manifestations   | 60 |
| 4.2.4.4 | Molecular Genetics  | 61 |
| 4.2.4.5 | LHON-Associated Mitochondrial Mutations                           | 62 |
| 4.2.4.6 | Genotype-Phenotype Correlation                                    | 62 |
| 4.2.4.7 | Evidence for an X-Linked Susceptibility Factor                    | 63 |

|         |   |    |
|---------|---|----|
| 4.2.4.8 | The Pathophysiology of LHON   | 63 |
| 4.3     | Primary Inherited Optic Neuropathies with Significant Systemic Features | 64 |
| 4.3.1   | Autosomal-Dominant Optic Atrophy and Neurological Defects               | 64 |
| 4.3.2   | Autosomal-Recessive Optic Atrophy "Plus"                                | 64 |
| 4.3.3   | Costeff's Syndrome  | 64 |
| 4.3.4   | Behr's Syndrome   | 64 |
| 4.3.5   | Wolfram Syndrome, DIDMOAD   | 64 |
| 4.4     | Conclusions   | 65 |

## Chapter 5

### Optic Nerve Tumours

Tim D. Matthews

|         |                              |    |
|---------|------------------------------|----|
| 5.1     | Introduction                 | 69 |
| 5.1.1   | Gliomas                      | 69 |
| 5.1.1.1 | NF1                          | 71 |
| 5.1.2   | Meningiomas                  | 71 |
| 5.1.2.1 | Retino-Choroidal Collaterals | 72 |
| 5.2     | Imaging                      | 74 |
| 5.2.1   | Gliomas                      | 74 |
| 5.2.1.1 | Typical                      | 74 |
| 5.2.1.2 | Masquerade                   | 74 |
| 5.2.2   | Meningiomas                  | 75 |
| 5.2.2.1 | Typical                      | 75 |
| 5.2.2.2 | Masquerade                   | 76 |
| 5.3     | Management                   | 76 |
| 5.3.1   | Gliomas                      | 76 |
| 5.3.1.1 | Paediatric                   | 77 |
| 5.3.1.2 | Adult                        | 78 |
| 5.3.2   | Meningiomas                  | 79 |
| 5.4     | Conclusions                  | 80 |

## Chapter 6

### Traumatic Optic Neuropathy: Recommendations and Neuroprotection

Solon Thanos, Stephan Grewe, Tobias Stupp

|       |                            |    |
|-------|----------------------------|----|
| 6.1   | Introduction               | 83 |
| 6.1.1 | Optic Nerve Anatomy        | 83 |
| 6.1.2 | Traumatic Optic Neuropathy | 84 |

|       |   |    |         |   |     |
|-------|---|----|---------|---|-----|
| 6.2   | Review of Previous Studies on TONs            | 84 | 7.3.1   | Scanning Laser Ophthalmoscopy and Tomography  | 103 |
| 6.3   | Histopathology of TON                         | 87 | 7.3.1.1 | The Rodenstock System   | 105 |
| 6.4   | Mechanisms of TON-Induced Ganglion Cell Death | 89 | 7.3.1.2 | The Heidelberg Laser Tomographic Scanner  | 105 |
| 6.5   | Diagnosis of TON                              | 89 | 7.3.1.3 | The Zeiss Confocal Scanning Laser Ophthalmoscope and TopSS™ Topographic Scanning System | 106 |
| 6.6   | Therapeutic Concepts of TON                   | 91 | 7.3.2   | The Heidelberg Retinal Tomograph II   | 106 |
| 6.6.1 | Steroids                                      | 91 | 7.3.3   | Scanning Laser Polarimetry ("GDx")  | 107 |
| 6.6.2 | Neuroprotection                               | 91 | 7.3.4   | Optical Coherence Tomography  | 109 |
| 6.6.3 | Surgical Decompression                        | 91 | 7.3.4.1 | Using OCT for Glaucoma Evaluation   | 111 |
| 6.6.4 | The Role of Ophthalmologists                  | 91 | 7.3.4.2 | Other Uses of OCT   | 111 |
| 6.7   | Outlook on Regeneration of the Optic Nerve    | 92 | 7.3.4.3 | Ultrahigh-Resolution OCT (UHR-OCT)  | 112 |
| 6.8   | Current Clinical Practice and Recommendations | 93 | 7.4     | Imaging of the Optic Nerve and Alzheimer Disease  | 113 |

## Part II Investigations

### Chapter 7

#### Imaging the Nerve Fiber Layer and Optic Disc

Marc Dinkin, Michelle Banks,  
Joseph F. Rizzo III

|         |   |     |
|---------|---|-----|
| 7.1     | Introduction  | 100 |
| 7.2     | Overview of Early Imaging Techniques                                    | 100 |
| 7.2.1   | Optic Nerve Head Drawings   | 100 |
| 7.2.2   | Direct Ophthalmoscopy of the Nerve Fiber Layer                          | 100 |
| 7.2.3   | Retinal Nerve Fiber Layer Photography                                   | 100 |
| 7.2.4   | Stereoscopic Optic Nerve Head Photography                               | 101 |
| 7.2.5   | Optic Nerve Head Analyzers  | 102 |
| 7.2.5.1 | The Topcon IMAGENet   | 102 |
| 7.2.5.2 | The Humphrey Retinal Analyzer   | 102 |
| 7.2.5.3 | The Rodenstock Optic Nerve Head Analyzer                                | 102 |
| 7.2.5.4 | The Glaucoma-Scope  | 103 |
| 7.3     | Modern Techniques for Optic Nerve and Retinal Nerve Fiber Layer Imaging | 103 |

|       |                      |     |
|-------|----------------------|-----|
| 7.5   | Comparing Modalities | 113 |
| 7.5.1 | MRI                  | 114 |
| 7.6   | Conclusion           | 115 |

### Chapter 8

#### Functional Neuroanatomy of the Human Visual System: A Review of Functional MRI Studies

Mark W. Greenlee, Peter U. Tse

|     |   |     |
|-----|---|-----|
| 8.1 | Introduction  | 119 |
| 8.2 | Imaging the Lateral Geniculate Nucleus                                    | 121 |
| 8.3 | Functional Maps of the Visual Field                                       | 121 |
| 8.4 | Striate and Extrastriate Visual Areas in Human Visual Cortex (V1, V2, V3) | 121 |
| 8.5 | Receptive Field Size as a Function of Retinal Eccentricity                | 122 |
| 8.6 | Alternative Methods of Retinotopic Mapping                                | 124 |
| 8.7 | Columnar Structures within Human V1                                       | 125 |
| 8.8 | Orientation Specificity of BOLD Responses in Visual Cortex                | 125 |

8.9 Visual Maps of Higher Visual Function: V4 ..... 126

8.10 Visual Maps of Higher Visual Function: V3A, V3B and KO 126

8.11 Segmenting Extrastriate Areas and MT+ into Functional Subregions ..... 127

8.12 Responses to Optic Flow ... 128

8.13 Disparity and Motion-in-Depth Stimulation ..... 129

8.14 Interface Between Visual and Oculomotor Systems ..... 129

8.15 Parietal Lobe Maps of Visuotopic Space ..... 130

8.16 Working Memory for Visual Stimuli ..... 130

8.17 Role of V1 in Visual Consciousness ..... 132

8.18 Summary ..... 132

**Chapter 9**  
**Investigating Visual Function with Multifocal Visual Evoked Potentials**

Michael B. Hoffmann

9.1 Introduction ..... 139

9.2 Multifocal Principle and Characteristics of Multifocal VEPs ..... 140

9.2.1 Basics – Multifocal Stimulation, First- and Second-Order Kernels 140

9.2.2 Stimulus Display for mfVEP Recordings ..... 143

9.2.3 Recording mfVEPs and Practical Considerations ..... 143

9.2.4 Dependence of mfVEPs on Visual Cortex Morphology ..... 146

9.3 Assessment of mfVEPs ..... 148

9.3.1 Response Magnitude ..... 148

9.3.2 Response Latency ..... 149

9.4 mfVEP Investigations of Diseases ..... 151

9.4.1 mfVEP in Glaucoma ..... 152

9.4.2 mfVEP in Optic Neuritis ... 153

9.4.3 mfVEP in Albinism ..... 154

9.5 Conclusion ..... 157

**Part III Retinal Disorders**

**Chapter 10**  
**Autoimmune Retinopathies**

Jennifer K. Hall, Nicholas J. Volpe

10.1 Autoimmune Disease Overview ..... 163

10.2 Autoimmune Retinopathy Overview ..... 164

10.3 Paraneoplastic Retinopathies ..... 164

10.3.1 Cancer-Associated Retinopathy ..... 164

10.3.1.1 Clinical Presentation ..... 166

10.3.1.2 Diagnostic Studies ..... 166

10.3.1.3 Pathophysiology ..... 166

10.3.1.4 Treatment ..... 168

10.3.2 Melanoma-Associated Retinopathy ..... 168

10.3.2.1 Clinical Presentation ..... 168

10.3.2.2 Diagnostic Studies ..... 168

10.3.2.3 Pathophysiology ..... 169

10.3.2.4 Treatment ..... 169

10.3.3 Bilateral Diffuse Uveal Melanocytic Proliferation .. 169

10.3.3.1 Clinical Presentation ..... 170

10.3.3.2 Diagnostic Studies ..... 170

10.3.3.3 Pathophysiology ..... 170

10.3.3.4 Treatment ..... 171

10.4 Autoimmune-Related Retinopathy and Optic Neuropathy ..... 171

10.5 Acute Outer Retinopathies with Blind Spot Enlargement ..... 172

10.5.1 Acute Idiopathic Blind Spot Enlargement ... 173

10.5.1.1 Clinical Presentation ..... 173

10.5.1.2 Diagnostic Studies ..... 173

10.5.1.3 Pathophysiology ..... 173

10.5.1.4 Treatment ..... 176

10.5.2 Multiple Evanescent White Dot Syndrome ..... 176

10.5.2.1 Clinical Presentation ..... 176

10.5.2.2 Diagnostic Studies ..... 176

10.5.2.3 Pathophysiology ..... 177

10.5.2.4 Treatment ..... 178

10.5.3 Acute Zonal Occult Outer Retinopathy ..... 178

10.5.3.1 Clinical Presentation ..... 178  
 10.5.3.2 Diagnostic Studies ..... 178  
 10.5.3.3 Pathophysiology ..... 179  
 10.5.3.4 Treatment ..... 179  
 10.5.3.5 AZOOR Complex of Disease 179  
 10.6 Summary ..... 180

**Chapter 11**  
**Retinal Research: Application to Clinical Practice**

Ludwig Aigner, Claudia Karl

11.1 Introduction ..... 185  
 11.1.1 Retinitis Pigmentosa ..... 185  
 11.1.2 Age-Related Macular Degeneration ..... 186  
 11.1.3 Glaucoma ..... 186  
 11.2 Cell Death in the Retina .... 186  
 11.2.1 Major Characteristics and Pathways of Apoptosis 187  
 11.2.1.1 Caspase-Dependent Apoptosis ..... 187  
 11.2.1.2 Caspase-Independent Apoptosis ..... 188  
 11.3 Therapeutic Strategies in Degenerative Retinal Diseases ..... 189  
 11.3.1 Strategies for Neuroprotection ..... 189  
 11.3.1.1 Animal Models in Retinal Degeneration Research .... 189  
 11.3.1.2 Strategies for Neuroprotection Interfering with the Induction Phase of Apoptosis ..... 190  
 11.3.1.3 Strategies for Neuroprotection Interfering with the Early Phase of Apoptosis ..... 191  
 11.3.1.4 Strategies Using Neuroprotective Cytokines that Showed Effects in Other Tissues ..... 191  
 11.3.2 Cell Therapy for the Diseased Retina .... 192  
 11.3.2.1 Cell Transplantation in the Retina ..... 193  
 11.3.2.2 Application of Transgenes or Genetically Engineered Stem and Progenitor Cells 198

11.3.2.3 Endogenous Cell Replacement in the Retina 199

**Part IV Systemic disease**

**Chapter 12**  
**Chorioretinal Lesions in Infectious Diseases of Neuroophthalmic Interest**

Yan Guex-Crosier

12.1 Introduction ..... 206  
 12.2 Ocular Zoonosis ..... 206  
 12.2.1 Ocular Toxoplasmosis ..... 206  
 12.2.1.1 Congenital Toxoplasmosis .. 206  
 12.2.1.2 Reactivation of Toxoplasmosis in Immunocompetent Patients ..... 207  
 12.2.1.3 Ophthalmic Toxoplasmosis in AIDS Patients ..... 209  
 12.2.1.4 Neurologic Manifestation of Toxoplasmosis in AIDS Patients ..... 209  
 12.2.1.5 Radiologic Manifestation of Toxoplasmosis in AIDS ... 209  
 12.2.2 Toxocariasis ..... 210  
 12.2.2.1 Introduction ..... 210  
 12.2.2.2 Ocular Manifestations ..... 210  
 12.2.2.3 Neurologic Manifestations 210  
 12.2.3 Diseases Transmitted by Ticks ..... 210  
 12.2.3.1 Introduction ..... 210  
 12.2.3.2 Tick-Borne Encephalitis .... 210  
 12.2.3.3 Lyme Disease ..... 211  
 12.2.4 Cat Scratch Disease ..... 214  
 12.2.4.1 Introduction ..... 214  
 12.2.4.2 Ocular and Neuroophthalmologic Manifestations ..... 214  
 12.2.4.3 Neurologic Manifestations 215  
 12.2.4.4 Therapy ..... 215  
 12.3 Sexually Transmitted Diseases ..... 215  
 12.3.1 Syphilis ..... 215  
 12.3.1.1 Introduction ..... 215  
 12.3.1.2 Ocular and Neuroophthalmologic Manifestations ..... 215  
 12.3.1.3 Diagnostic Tests ..... 216

12.3.1.4 Therapy ..... 216

12.3.2 Human Immunodeficiency Virus (HIV) and Ocular Infection ..... 216

12.3.2.1 Introduction ..... 216

12.3.2.2 HIV Retinopathy ..... 217

12.3.2.3 CMV Retinitis ..... 218

12.4 Encephalopathies Due to Viral and Non-Conventional Agents ..... 220

12.4.1 Lymphocytic Choriomeningitis Virus .... 220

12.4.2 Creutzfeldt–Jakob Disease ..... 220

12.4.3 JC Virus and Progressive Multifocal Leukoencephalopathy ..... 221

12.4.4 Herpetic Encephalopathy and Acute Retinal Necrosis Syndrome ..... 222

12.5 Conclusion ..... 222

**Chapter 13**  
**Giant Cell Arteritis**

Aki Kawasaki

13.1 Pathophysiology of Giant Cell Arteritis ..... 227

13.1.1 Epidemiology ..... 227

13.1.2 Triggering Event ..... 228

13.1.3 Tropism to Certain Vascular Beds ..... 228

13.1.4 Macrophage Recruitment and Vascular Injury ..... 229

13.1.5 Systemic Inflammation .... 230

13.2 Clinical (Non-Ophthalmic) Manifestations of GCA ..... 231

13.2.1 Natural History ..... 231

13.2.2 Systemic Signs and Symptoms ..... 231

13.2.3 Headache and Craniofacial Pain ..... 231

13.2.4 Auditory Manifestations ... 232

13.2.5 Neurologic Manifestations 232

13.2.6 Occult GCA ..... 232

13.3 Visual Manifestations of GCA ..... 233

13.3.1 Transient Visual Loss ..... 233

13.3.2 Anterior Ischemic Optic Neuropathy ..... 234

13.3.3 Other Types of Ischemic Visual Loss ..... 235

13.3.4 Diplopia ..... 235

13.3.5 Orbital Manifestations ..... 236

13.4 Clinical Subtypes of GCA ... 236

13.4.1 Systemic Inflammatory Syndrome ..... 236

13.4.2 Cranial Arteritis ..... 236

13.4.3 Large-Vessel Vasculitis ..... 237

13.5 Laboratory Investigations in GCA ..... 238

13.5.1 Erythrocyte Sedimentation Rate ..... 238

13.5.2 C-Reactive Protein ..... 239

13.5.3 Thrombocytosis ..... 239

13.5.4 Interleukin-6 and Other Cytokines ..... 239

13.5.5 Anemia ..... 240

13.5.6 Others ..... 240

13.6 Diagnosis of GCA ..... 240

13.6.1 Temporal Artery Biopsy .... 241

13.6.2 American College of Rheumatology Criteria .. 241

13.6.3 Role of Ultrasound ..... 243

13.6.4 Other Non-Invasive Imaging of the Cranial Arteries ..... 243

13.7 Treatment and Prognosis of GCA ..... 244

13.7.1 Corticosteroids ..... 244

13.7.1.1 Starting Dose ..... 245

13.7.1.2 Maintenance Dose ..... 245

13.7.1.3 Tapering Regimen ..... 245

13.7.1.4 Duration of Treatment ..... 245

13.7.2 Visual Outcome on Corticosteroids ..... 245

13.7.3 Methotrexate ..... 246

13.7.4 Other Adjuvant Therapies .. 246

13.7.5 Treatment of Large-Vessel Involvement ..... 247

**Part V Oculomotility**

**Chapter 14**  
**Cerebral Control of Eye Movements**

Charles Pierrot-Deseilligny

14.1 Introduction ..... 254

14.2 Brainstem ..... 255

14.2.1 Horizontal Eye Movements 255  
 14.2.1.1 Final Common Pathway .... 255  
 14.2.1.2 Premotor Structures and Afferent Pathways .... 257  
 14.2.2 Vertical Eye Movements .... 259  
 14.2.2.1 Final Common Pathway .... 259  
 14.2.2.2 Premotor Structures and Brainstem Afferents ... 259  
 14.3 Suprareticular Structures ... 261  
 14.3.1 Cerebellum ..... 261  
 14.3.2 Cerebral Hemispheres ..... 262  
 14.4 Abnormal Eye Movements 263  
 14.4.1 Nystagmus ..... 263  
 14.4.2 Non-Nystagmic Abnormal Eye Movements ..... 264

**Chapter 15**  
**Chronic Progressive External Ophthalmoplegia – A Common Ocular Manifestation of Mitochondrial Disorders**

Marcus Deschauer, Stephan Zierz

15.1 Introduction ..... 267  
 15.2 Clinical Features ..... 268  
 15.2.1 Ophthalmoplegia and Ptosis ..... 268  
 15.2.2 CPEO Plus: Multisystemic Involvement ..... 268  
 15.2.2.1 Muscle Impairment ..... 268  
 15.2.2.2 Visual Impairment ..... 268  
 15.2.2.3 Specific CPEO Plus Syndromes ..... 268  
 15.3 Genetics ..... 270  
 15.3.1 General Mitochondrial Genetics ..... 270  
 15.3.2 Single Deletions of mtDNA 270  
 15.3.3 Defects of Intergenomic Communication with Multiple Deletions of mtDNA ..... 271  
 15.3.4 Point Mutations of mtDNA ..... 272  
 15.3.5 Coenzyme Q Deficiency .... 273  
 15.3.6 Genotype–Phenotype Correlation ..... 273  
 15.4 Diagnostics ..... 274  
 15.4.1 Myohistological Investigations ..... 275  
 15.4.2 Biochemical Investigations 275

15.4.3 Molecular Genetic Investigations ..... 275  
 15.5 Treatment ..... 276  
 15.5.1 Pharmacological Therapy .. 276  
 15.5.2 Symptomatic Treatment ... 277  
 15.5.3 Gene Therapy ..... 277  
 15.6 Differential Diagnosis ..... 278  
 15.6.1 Oculopharyngeal Muscular Dystrophy ..... 278  
 15.6.2 Myasthenic Syndromes .... 278  
 15.6.3 Congenital Fibrosis of the Extraocular Muscles 279  
 15.6.4 Ocular Myositis ..... 279  
 15.6.5 Endocrine Ophthalmopathy ..... 279  
 15.6.6 Myotonic Dystrophy ..... 279  
 15.6.7 Facioscapulohumeral Muscular Dystrophy ..... 279  
 15.6.8 Congenital Myopathies .... 279

**Chapter 16**  
**Treatment of Specific Types of Nystagmus**

Marianne Dieterich

16.1 Introduction ..... 284  
 16.2 Peripheral Vestibular and Ocular Motor Disorders 284  
 16.2.1 Acute Peripheral Vestibulopathy, Vestibular Neuritis ..... 284  
 16.2.1.1 Etiology ..... 286  
 16.2.1.2 Therapeutic Recommendations ..... 287  
 16.2.2 Superior Oblique Myokymia ..... 288  
 16.2.2.1 Etiology ..... 288  
 16.2.2.2 Therapeutic Recommendations ..... 288  
 16.3 Supranuclear Ocular Motor Disorders ..... 289  
 16.3.1 Central Vestibular Disorders 289  
 16.3.1.1 Vestibular Syndromes in the Sagittal (Pitch) Plane 289  
 16.3.2 Central Ocular Motor Disorders ..... 294  
 16.3.2.1 Acquired Pendular Nystagmus ..... 294  
 16.3.2.2 Opsoclonus and Ocular Flutter ..... 296

## Part VI Rehabilitation

### Chapter 17

#### Rehabilitation in Neuroophthalmology

Susanne Trauzettel-Klosinski

|          |  |            |
|----------|--|------------|
| 17.1     | Introduction   | 301        |
| 17.2     | Psychophysics of Normal Reading  | 302        |
| 17.3     | Diseases of the Visual Pathways and their Functional Deficits          | 303        |
| 17.3.1   | Optic Neuropathies   | 303        |
| 17.3.1.1 | Central Scotomas   | 303        |
| 17.3.1.2 | Arcuate Scotomas: Nerve Fiber Bundle Defects                           | 305        |
| 17.3.1.3 | Ring Scotomas  | 305        |
| 17.3.1.4 | Constricted Fields   | 305        |
| 17.3.1.5 | The Impact of Visual Field Defects on Reading Performance              | 305        |
| 17.3.2   | Optic Chiasmatal Syndromes   | 307        |
| 17.3.3   | Suprachiasmatic Lesions of the Visual Pathways                         | 307        |
| 17.3.3.1 | Hemianopic Reading Disorder  | 308        |
| 17.3.3.2 | Hemianopic Orientation Disorder  | 310        |
| 17.3.4   | Cortical Visual Impairment   | 311        |
| 17.4     | Diagnostic Procedures to Examine Reading Ability                       | 311        |
| 17.5     | Rehabilitation Programs  | 312        |
| 17.5.1   | Visual Aids in Reading Disorders                                       | 312        |
| 17.5.2   | Visual and Other Aids in Spatial Orientation Problems                  | 313        |
| 17.5.3   | Training   | 314        |
| 17.5.3.1 | Training for Patients with Circumscribed Scotomas in the Central Field | 314        |
| 17.5.3.2 | Training for Patients with Homonymous Field Defects                    | 315        |
| 17.5.4   | Counseling Regarding Public Support                                    | 316        |
| 17.6     | Summary and Conclusions  | 316        |
|          | <b>Subject Index</b>   | <b>321</b> |

# Contributors

## **Ludwig Aigner, Prof. Dr.**

Klinik und Poliklinik für Neurologie  
der Universität Regensburg  
Im Bezirksklinikum  
Universitätsstraße 84  
93053 Regensburg  
Germany

## **Anthony C. Arnold, MD, Prof.**

Neuro-Ophthalmology Division  
Director, UCLA Optic Neuropathy Center  
Jules Stein Eye Institute  
UCLA Department of Ophthalmology  
100 Stein Plaza  
Los Angeles, CA 90095-7005  
USA

## **Edward J. Atkins, MD**

Division of Neurology  
University of Saskatchewan  
RUH Box 239  
103 Hospital Drive  
Saskatoon, SK, S7N 0W8  
Canada

## **Michelle Banks, MD**

100 Stein Plaza  
Los Angeles, California  
USA

## **Valérie Biousse, MD, Prof.**

Departments of Ophthalmology and Neurology  
Emory University  
Neuro-ophthalmology Unit  
Emory Eye Center  
1365-B Clifton Road, NE, Atlanta, Georgia 30322  
USA

## **François-Xavier Borruat, MD, PD, MER**

Department of Neuro-Ophthalmology  
Hôpital Ophtalmique Jules Gonin  
Avenue de France 15  
CH-1004 Lausanne  
Switzerland

## **Marcus Deschauer, Priv.-Doz. Dr.**

Neurologische Klinik  
der Universität Halle-Wittenberg  
Ernst-Grube-Straße 40  
06097 Halle/Saale  
Germany

## **Marianne Dieterich, Prof. Dr.**

Neurologische Klinik, Universität Mainz  
Langenbeckstraße 1  
55101 Mainz  
Germany

## **Marc Dinkin, MD**

Brigham and Women's Hospital  
75 Francis Street  
Boston, MA 02115  
USA

## **Mark W. Greenlee, Prof. Dr.**

Institut für Experimentelle Psychologie  
Universität Regensburg  
Universitätsstraße 31  
93053 Regensburg  
Germany

## **Stephan Grewe, Dr.**

Institut für Experimentelle Ophthalmologie  
Klinik und Poliklinik für Augenheilkunde  
Domagkstraße 15  
48149 Münster  
Germany



**Yan Guex-Crosier, MD, PD, MER**

Ocular Immunology and Inflammation Unit  
Jules Gonin Eye Hospital  
15 av. de France  
CH 1004 Lausanne  
Switzerland

**Jennifer K. Hall, MD**

Scheie Eye Institute  
University of Pennsylvania Department  
of Ophthalmology  
51 North 39th Street  
Philadelphia, Pennsylvania 19104  
USA

**Michael B. Hoffmann, Dr.**

Universitäts-Augenklinik  
Visual Processing Laboratory  
Leipziger Straße 44  
39120 Magdeburg  
Germany

**Claudia Karl, Dr.**

Institut für Neurologie  
Universität Regensburg  
Germany

**Aki Kawasaki, MD, MER**

Department of Neuro-ophthalmology  
Hôpital Ophtalmique Jules Gonin  
Avenue de France 15  
1004 Lausanne  
Switzerland

**Birgit Lorenz, MD, FEBO, Prof.**

Klinik und Poliklinik für Augenheilkunde  
Universitätsklinikum Gießen und Marburg GmbH,  
Standort Gießen  
Friedrichstraße 18  
35392 Gießen  
Germany

**Tim D. Matthews, MBBS, FRCS, FRCOphth**

Department of Ophthalmology  
Selly Oak Hospital  
Raddlebarn Rd  
Birmingham B29 6 JD  
UK

**Nancy J. Newman, MD, Prof.**

Departments of Ophthalmology  
Neurology, and Neurological surgery  
Emory University, Neuro-ophthalmology Unit  
Emory Eye Center  
1365-B Clifton Road, NE, Atlanta Georgia 30322  
USA

**Charles Pierrot-Deseilligny, MD, Prof.**

Hôpital La Pitié-Salpêtrière  
47-83, Boulevard de l'Hôpital  
75651 Paris Cedex 13  
France

**Joseph F. Rizzo III, MD, Prof.**

Massachusetts Eye and Ear Infirmary  
Department of Neuro-Ophthalmology  
243 Charles Street, 9th FL  
Boston, MA 02114  
USA

**Tobias Stupp, PD, Dr.**

Institut für Experimentelle Ophthalmologie  
Klinik und Poliklinik für Augenheilkunde  
Domagkstraße 15  
48149 Münster  
Germany

**Solon Thanos, Prof. Dr.**

Institut für Experimentelle Ophthalmologie  
Klinik und Poliklinik für Augenheilkunde  
Domagkstraße 15  
48149 Münster  
Germany

**Susanne Trauzettel-Klosinski, Prof. Dr.**

Augenklinik der Universität Tübingen  
Schleichstraße 12–16  
72076 Tübingen  
Germany

**Peter U. Tse, Dr.**

Institute für Experimentelle Psychologie  
der Universität Regensburg  
93053 Regensburg  
Germany

**Nicholas J. Volpe, MD, Prof.**

Scheie Eye Institute  
University of Pennsylvania Department  
of Ophthalmology  
51 North 39th Street  
Philadelphia, Pennsylvania 19104  
USA

**Stephan Zierz, Prof., Dr.**

Neurologische Universitätsklinik  
Ernst-Grube-Straße 40  
06120 Halle (Saale)  
Germany

**Marcela Votruba, MA, BM, BCh, FRCOphth, PhD**

School of Optometry & Vision Science  
Cardiff University  
Maindy Road  
Cathays  
Cardiff CF24 4LU  
UK

Part I

# Optic Nerve

# Optic Neuritis and Multiple Sclerosis

Edward J. Atkins, Valérie Biousse, Nancy J. Newman

## Core Messages

- Idiopathic optic neuritis, an isolated inflammatory optic neuropathy secondary to demyelination, is the most common cause of optic neuropathy in the young and is often the first sign of multiple sclerosis (MS).
- It is now possible to predict the risk of subsequent MS in selected patients with optic neuritis, allowing the anticipatory use of immunomodulatory agents to reduce the risk and severity of MS in those patients.
- A number of recent studies have clarified the natural history of optic neuritis, the largest being the Optic Neuritis Treatment Trial (ONTT).
- The ONTT confirmed that spontaneous visual recovery begins rapidly (within 3 weeks) in about 80% of patients and continues for up to 1 year; if at least some improvement does not occur within 5 weeks, the diagnosis of idiopathic optic neuritis should be reconsidered.
- The initial magnetic resonance imaging (MRI) helps to stratify the risk of MS. In the ONTT, the 10-year risk of MS in patients with at least one MRI T2 lesion was 56%, as compared to 22% in those with a normal baseline MRI. A normal MRI in combination with painless optic neuritis, severe optic nerve head edema, peripapillary hemorrhages, or a macular star defines a very low MS risk subgroup.
- In the ONTT, treatment with a lower dose of oral corticosteroids (1 mg/kg per day) was associated with an increased risk of recurrent optic neuritis, with a 41% chance of recurrence at 5 years among patients who received oral prednisone, versus 25% for those who received high-dose intravenous methylprednisolone (1000 mg/day) or placebo.
- High-dose steroids hasten the rate, but not the final extent, of visual recovery in optic neuritis, and the decision to use this therapy should be individualized.
- Interferon beta-1a or beta-1b therapy should be considered in selected high-risk patients.

## 1.1 Idiopathic Optic Neuritis

### 1.1.1 Clinically Isolated Syndrome

Idiopathic optic neuritis is the most common cause of optic neuropathy in the young. It is an isolated inflammatory optic neuropathy secondary to demyelination, and is considered one of the clinically isolated syndromes suggestive of multiple sclerosis (MS) [28, 57]. Indeed, isolated acute optic neuritis is often the first sign of MS, and many patients with MS develop optic neuritis during the course of their disease [41, 42]. For many patients, carrying the diagnosis of “optic neuritis” is equivalent to having a “high risk of MS” [2]. It is therefore essential that the correct diagnosis be made in a young patient presenting with visual loss [59].

### 1.1.2 Clinical Features of Acute Idiopathic Optic Neuritis

Idiopathic optic neuritis is typically characterized by the following clinical characteristics [28, 57]:

- Young women (3-to-1 female-to-male ratio)
- Unilateral (rarely bilateral)
- Acute to subacute onset (usually rapidly progressive over a few days)
- Decreased visual acuity (variable)
- Decreased color vision (usually pronounced)
- Pain with eye movements (in >90% of cases)
- Exacerbation with heat or exercise (Uhthoff phenomenon)
- Absence of any systemic or neurologic symptoms

### 1.1.3 Examination Findings in Acute Idiopathic Optic Neuritis

- Relative afferent pupillary defect (if unilateral or asymmetric optic neuropathy)
- Funduscopy:
  - Normal optic nerve in the acute phase (in two-thirds of cases) or swollen optic nerve (in one-third of cases)

- Normal macula and retina (no exudates, no hemorrhages)
- Optic disc pallor (at least 4-6 weeks after onset)
- Visual field test: variable, but most often central scotoma
- MRI: depending on the quality of imaging, 50%–90% of patients with optic neuritis show enhancement of the optic nerve on orbital MRI; however, this finding is nonspecific [28, 57]

## Summary for the Clinician

- Familiarity with both the characteristic clinical features as well as the typical examination findings in idiopathic optic neuritis will greatly decrease the chance of misdiagnosing the cause of the visual loss, and overlooking the risk of MS.
- The optic nerve appears normal in the acute phase in about two-thirds of cases (retrobulbar optic neuritis), and is swollen in about one-third of cases (anterior optic neuritis or papillitis).
- In all cases, pallor of the disc develops only 4–6 weeks after the onset of visual loss.

## 1.2 Natural History of Acute Idiopathic Optic Neuritis

Some spontaneous visual recovery is a nearly universal feature of idiopathic acute optic neuritis, and the visual prognosis for these patients is usually excellent, regardless of treatment; however, the risk of subsequent development of MS after an isolated attack of idiopathic optic neuritis has been estimated as high as 74% at 15 years [22, 24, 31, 35, 43, 60].

### 1.2.1 Important Studies

The natural history of optic neuritis has been clarified by a number of recent studies, among which

the Optic Neuritis Treatment Trial (ONTT) [6] is the largest. Natural history data have been collected from a long-term prospective study carried out in Boston [12], from a Queens Square study in London [16], from a prospective study performed in Barcelona [71], and from several clinical trials involving immunomodulatory drugs [9, 15, 16, 18, 26, 31, 56]. Data from these studies have contributed to our understanding of the natural history of optic neuritis. The study descriptions and results are summarized in Table 1.1.

### 1.2.2 Visual Prognosis

The ONTT confirmed that spontaneous visual recovery begins rapidly (within 3 weeks) in about 80% of patients with idiopathic acute optic neuritis, and continues for up to 1 year [50, 52]. The ONTT also emphasized that if at least some improvement does not occur within 5 weeks, the diagnosis of idiopathic optic neuritis should be reconsidered. At 1-year follow-up almost all patients had visual acuity in the affected eye of better than 20/40, and half of patients had visual acuity of at least 20/20 (see Table 1.2). Nevertheless, a majority of patients complained of permanent visual dysfunction including [50, 52]:

- Impaired contrast sensitivity
- Decreased color vision
- Difficulty with motion perception
- Diminished intensity of light

Following optic neuritis, patients often also experience Uhthoff phenomenon, a transient visual decline following exposure to heat or exertion.

Although intravenous corticosteroids hasten visual recovery, visual outcome at 6 months was the same for all treatment groups. Indeed, a meta-analysis of 12 randomized controlled trials of steroid treatment in MS and optic neuritis confirmed that although corticosteroids were effective in improving short-term visual recovery, there was no statistically significant benefit in long-term outcome [14].

### Summary for the Clinician

- Some spontaneous visual recovery is a nearly universal feature of idiopathic acute optic neuritis, and the visual prognosis of these patients is usually excellent, regardless of treatment.
- Intravenous steroids hasten visual recovery, but have no effect on final visual outcome.

### 1.2.3 Risk of Recurrence of Optic Neuritis

In the ONTT, the probability of recurrence of optic neuritis in either eye was 35 % at 10 years [52]. Treatment with oral corticosteroids was associated with an increased risk of recurrent optic neuritis. In fact, as shown in Table 1.2, patients who received low-dose oral prednisone had the highest rate of recurrence at 5 years compared to those who received intravenous methylprednisolone or placebo [50]. At 10 years, the recurrence risk was still higher when compared to the methylprednisolone and placebo groups [52].

### Summary for the Clinician

- Oral corticosteroids in conventional doses of 1 mg/kg per day may increase the risk of recurrence, and should not be used in the treatment of acute idiopathic optic neuritis.

### 1.2.4 Risk of Developing Multiple Sclerosis

Even prior to the advent of MRI, several studies had emphasized the risk of developing MS following an episode of isolated optic neuritis [22, 24, 35, 40, 59]. Subsequent studies have shown that brain MRI is the most powerful predictor of MS in patients with acute idiopathic optic neuritis [8, 9, 13, 15, 16, 18, 26, 29, 31, 40, 46, 47,

**Table 1.1.** Summary of large studies evaluating the natural history and management of idiopathic acute optic neuritis. (*BENEFIT* Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment Study, *CHAMPS* Controlled High Risk Avonex Multiple Sclerosis Study, *ETOMS* Early Treatment of Multiple Sclerosis Study, *LONS* Longitudinal Optic Neuritis Study, *ON* optic neuritis, *ONTT* Optic Neuritis Treatment Trial)

| Study name                            | Period of enrolment | Patient number | Type of study  | Methods  | Follow-up (years) | Risk of clinically definite MS   |
|---------------------------------------|---------------------|----------------|--|--|-------------------|--|
| Boston (Rizzo and Lessell 1988) [60]  | 1973–1988           | 60 (all ON)    | Observational study; long-term prospective; natural history  | Follow-up of a group of patients with isolated optic neuritis. No MRI data   | 15                | 74% of women; 34% of men   |
| Sweden (Söderström et al. 1998) [68]  | 1990–1995           | 116 (all ON)   | Observational study; short-term prospective; natural history | Follow-up of a group of patients with isolated optic neuritis. A baseline MRI was obtained   | 2.1               | Normal MRI: 6%; abnormal MRI: 34.5%; ( $\geq 3$ lesions)                                       |
| Milan (Ghezzi et al. 1999) [29]       | 1982–1993           | 102 (all ON)   | Observational study; long-term prospective; natural history  | Follow-up of a group of patients with isolated optic neuritis in a serial MRI study  | 8–10              | Normal MRI: 0%; abnormal MRI: 52.1%; ( $\geq 1$ lesion)  |
| Queens Square (Brex et al. 2002) [13] | 1988–2002           | 71 (36 ON)     | Observational study; long-term prospective; natural history  | Follow-up of a group of patients with clinically isolated syndromes in a serial MRI study  | 14                | Normal MRI: 19%; abnormal MRI: 88%; ( $\geq 1$ lesion)   |
| Barcelona (Tintoré et al. 2005) [71]  | 1995–2004           | 320 (123 ON)   | Observational study; short-term prospective; natural history | Follow-up of a group of patients with clinically isolated syndromes in a serial MRI study (using MRI component of McDonald criteria)   | 2–3               | Normal MRI: 5.9%; abnormal MRI: 55%  |
| ONTT/LHONS [6, 51, 52, 53, 54]        | 1988–1991           | 388 (all ON)   | Randomized double-blind                                      | Randomization in 3 arms: (1) IV methylprednisolone (250 mg q 6 h for 3 days), followed by oral prednisone (1 mg/kg per day for 11 days); (2) oral prednisone alone (1 mg/kg per day for 14 days); (3) oral placebo | 10                | Normal MRI: 22%; abnormal MRI: 56%; ( $\geq 1$ lesion); no difference between treatment groups |

Adapted from Atkins EJ, Biouesse V, Newman NJ (2006) The natural history of optic neuritis. *Rev Neurol Dis* 3:45–55 [3].

**Table 1.1.** (*continued*) Summary of large studies evaluating the natural history and management of idiopathic acute optic neuritis. (*BENEFIT* Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment Study, *CHAMPS* Controlled High Risk Avonex Multiple Sclerosis Study, *ETOMS* Early Treatment of Multiple Sclerosis Study, *LONS* Longitudinal Optic Neuritis Study, *ON* optic neuritis, *ONTT* Optic Neuritis Treatment Trial)

| Study name                                      | Period of enrolment | Patient number | Type of study           | Methods  | Follow-up (years) | Risk of clinically definite MS   |
|---|---------------------|----------------|-------------------------|--|-------------------|--|
| CHAMPS/CHAMPIONS [15, 16]                       | 1996–1998           | 383 (192 ON)   | Randomized double-blind | Randomization of high-risk patients with a clinically isolated syndrome ( $\geq 2$ MRI lesions) to (1) interferon beta-1a (Avonex*) (30 $\mu\text{g}$ IM) or (2) placebo                                 | 3                 | All with abnormal MRI ( $\geq 2$ lesions); 35% in interferon group; 50% in placebo group |
| ETOMS (Comi et al. 2001) [18]                   | 1995–1997           | 309 (98 ON)    | Randomized double-blind | Randomization of high-risk patients with a clinically isolated syndrome ( $\geq 2$ MRI lesions) to (1) interferon beta-1a (Rebif®) (22 $\mu\text{g}$ SC weekly for 2 years) or (2) placebo               | 2                 | All with abnormal MRI ( $\geq 4$ lesions); 34% in interferon group; 45% in placebo group |
| BENEFIT (Freedman and colleagues 2006) [26, 56] | 2004–2006           | 487 (80 ON)    | Randomized double-blind | Randomization of high-risk patients with a clinically isolated syndrome ( $\geq 2$ MRI lesions) to (1) interferon beta-1b (Betaseron*) (250 $\mu\text{g}$ SC every other day for 2 years) or (2) placebo | 2                 | All with abnormal MRI ( $\geq 2$ lesions); 28% in interferon group; 45% in placebo group |

Adapted from Atkins EJ, Bioussé V, Newman NJ (2006) The natural history of optic neuritis. *Rev Neurol Dis* 3:45–55 [3].



**Table 1.2.** Summary of results from the Optic Neuritis Treatment Trial

| Visual prognosis [50, 52]                                   |                            |                             |
|---|----------------------------|-----------------------------|
| Visual acuity (affected eye)                                | 1-year results (% , n=454) | 10-year results (% , n=319) |
| 20/40 or better   | 95                         | 91                          |
| 20/20 or better   | 50                         | 69                          |
| Risk of recurrence of optic neuritis in either eye [50, 52] |                            |                             |
| Treatment group   | 5-year follow-up (%)       | 10-year follow-up (%)       |
| Oral prednisone (1 mg/kg)                                   | 41                         | 44                          |
| IV methylprednisolone                                       | 25                         | 29                          |
| Placebo   | 25                         | 31                          |
| Development of multiple sclerosis [49, 51]                  |                            |                             |
| Treatment group   | 5-year follow-up (%)       |                             |
| Oral prednisone (1 mg/kg)                                   | 32                         |                             |
| IV methylprednisolone                                       | 27                         |                             |
| Placebo   | 31                         |                             |
| Overall   | 30                         |                             |
| Brain MRI at baseline                                       | 10-year follow-up (%)      |                             |
| No lesion   | 22                         |                             |
| One lesion  | 52                         |                             |
| > one lesion  | 56                         |                             |
| Overall   | 38                         |                             |

49, 51, 54, 56, 68]. This is in accordance with the recent modification of MS diagnostic criteria, which now include MRI changes (Table 1.3) [5, 19, 34, 39, 55]. Several important studies have defined the risk of developing MS, and the results are shown in Tables 1.1 and 1.2.

The ONTT did not show any demographic or clinical features of optic neuritis predictive of MS development among patients with an abnormal baseline MRI. However, in patients with a normal baseline MRI, the risk of developing MS was 3 times lower for men than for women. The risk was also lower for those who had optic nerve head edema (anterior optic neuritis) (Table 1.4).

It has been suggested that patients with MS who initially present with acute optic neuro-

tis have a better long-term prognosis regarding conversion to MS than those who present with another clinically isolated syndrome [41, 42, 71]. Tintoré et al. [71] propose that the reason why isolated optic neuritis patients may have a smaller risk for conversion to MS is because they more often have a normal baseline MRI than patients with other clinically isolated syndromes. They emphasized that if a patient with optic neuritis has abnormal baseline MRI results, his or her prognosis for MS conversion does not differ from that of other patients with different clinically isolated syndromes. Similarly, the CHAMPS [16] and ETOMS [18] trials found no differences in clinical or MRI behavior between their clinically isolated syndrome groups and their placebo groups.

**Table 1.3.** The 2005 revised McDonald criteria for the diagnosis of multiple sclerosis. (CSF cerebrospinal fluid, MRI magnetic resonance imaging, MS multiple sclerosis)

| Clinical presentation  | Additional data needed for MS diagnosis  |
|--|--|
| Two or more attacks with objective evidence of two or more lesions                       | None   |
| Two or more attacks with objective evidence of one lesion                                | Dissemination in space demonstrated by MRI <sup>a</sup> , <i>or</i> two or more lesions characteristic of MS on MRI <i>with</i> positive CSF (oligoclonal bands or raised IgG index) |
| One attack with objective clinical evidence of two or more lesions                       | Dissemination in time demonstrated by MRI <sup>b</sup> , <i>or</i> await a second clinical attack  |
| One attack with objective clinical evidence of one lesion (clinically isolated syndrome) | Dissemination in space demonstrated by MRI, <i>or</i> two or more lesions characteristic of MS <i>with</i> positive CSF  |
| Insidious neurological progression suggestive of MS                                      | Positive CSF <i>and</i> dissemination in space <i>and</i> time demonstrated by MRI, <i>and</i> continued progression for at least 1 year   |

<sup>a</sup>MRI lesions disseminated in space: at least three of the following:

1. One gadolinium-enhancing lesion or nine T2-hyperintense lesions (see Fig. 1.2).
2. At least one infratentorial lesion (includes brainstem and spinal cord).
3. At least one juxtacortical lesion.
4. At least three periventricular lesions.

<sup>b</sup>MRI lesions disseminated in time: at least one of the following:

1. If MRI is obtained more than 3 months after the clinical event, then a gadolinium-enhancing lesion at a site different from the original clinical event is sufficient. If there is no gadolinium enhancement, then a follow-up scan must be done more than 3 months later. A new T2 or gadolinium-enhancing lesion on the subsequent MRI fulfills the requirement.
2. If MRI is obtained less than 3 months after the onset of the clinical event, then a second scan more than 3 months later showing a new gadolinium-enhancing lesion fulfills the requirement. If no gadolinium-enhancing lesion is seen on the second scan, a further scan obtained more than 3 months after the first scan that shows a new gadolinium-enhancing lesion, or a new T2 hyperintense lesion, fulfills the requirement

Data from Barkhof et al. [5], McDonald et al. [39], Polman et al. [55], and Tintoré et al. [70].

**Table 1.4.** Features associated with subsequent development of MS in the ONTT patients who had a normal baseline MRI (191 patients)

|                       | <i>N</i> | 10-year risk of MS (%) | Hazard ratio | 95% CI    | <i>p</i> |
|-----------------------|----------|------------------------|--------------|-----------|----------|
| Overall               | 191      | 22                     |              |           |          |
| Gender                |          |                        |              |           |          |
| Women                 | 142      | 25                     | 1.00         | 0.12–0.98 | 0.05     |
| Men                   | 49       | 10                     | 0.35         |           |          |
| Optic disc appearance |          |                        |              |           |          |
| Normal                | 110      | 28                     | 1.00         | 0.20–0.84 | 0.01     |
| Edema                 | 81       | 14                     | 0.41         |           |          |
| Pain                  |          |                        |              |           |          |
| Yes                   | 173      | 24                     | 1.00         |           |          |
| No                    | 18       | 0                      |              |           |          |

Data from Optic Neuritis Study Group (2003) High risk and low risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the Optic Neuritis Treatment Trial. Arch Ophthalmol 121:944–949 [51].

### Summary for the Clinician

- The risk of subsequent development of MS after an isolated attack of idiopathic optic neuritis has been estimated to be as high as 74% at 15 years.
- In the ONTT, the overall risk of development of clinically definite MS was 30% at 5 years, 38% at 10 years, and 40% at 12 years.
- The ONTT showed no significant difference among treatment groups (low-dose oral steroid versus high-dose intravenous steroid versus placebo) in terms of the eventual development of clinically definite MS.
- Studies comparing interferon treatment with placebo show a modest but consistent reduction in the risk of developing subsequent MS in high-risk patients with an abnormal MRI.
- Brain MRI is the most powerful predictor of MS in patients with idiopathic optic neuritis.
- MRI at baseline, not clinically isolated syndrome topography, is the crucial issue at MS presentation.

### 1.2.5 Severity of Multiple Sclerosis in Patients Presenting with Optic Neuritis

Studies have garnered some conflicting data regarding this issue. It has been suggested that optic neuritis patients who eventually develop MS have a better neurologic prognosis (less neurologic disability) than those presenting with another clinically isolated syndrome (such as brainstem or spinal cord syndromes) (Table 1.5) [53, 74].

### Summary for the Clinician

- Optic neuritis patients who ultimately develop MS may have a better neurologic prognosis than those who present with other clinically syndromes.

### 1.3 Management of Acute Idiopathic Optic Neuritis

Although guidelines regarding the early management of acute optic neuritis with corticosteroids were published a few years ago [33], controversy

**Table 1.5.** Neurologic impairment after optic neuritis. The Expanded Disability Status Scale (EDSS) is used for rating impairment and disability in MS. It is a 20-step ordinal scale that ranges between 0.0 (normal status) and 10.0 (death due to MS). It is graded according to the findings of a standard neurologic examination summarized into several functional systems. It has been widely used in clinical trials of MS as a measure of disease progression

| Study               | Years of follow-up | Percentage of patients (%) | EDSS score (Expanded Disability Status Scale) | Comments   |
|---------------------|--------------------|----------------------------|---|--|
| ONTT [53]           | 10                 | 65                         | <3  | All optic neuritis patients  |
| Boston [60]         | 15                 | 83                         | <3  | All optic neuritis patients  |
| Queen's Square [13] | 14.1               | 68                         | >3  | Includes optic neuritis patients and spinal cord/brainstem syndromes |
| London, ON [74]     | 12                 | 57                         | >3  | Includes optic neuritis patients and spinal cord/brainstem syndromes |

remains regarding the optimal long-term treatment and follow-up of patients with acute idiopathic optic neuritis [34]. Careful assessment of the risk for the subsequent development of MS should be individualized using clinical examination (including detailed ophthalmologic examination) and brain MRI (Table 1.3) [2].

### 1.3.1 Diagnosis

The diagnosis of optic neuritis is mostly clinical. Indeed, the ONTT showed that routine blood tests including antinuclear antibodies, angiotensin-converting enzyme, syphilis testing, and chest X-ray were of no value in typical cases [7]. Visual-evoked potentials are only useful when the diagnosis of optic neuritis is uncertain [57].

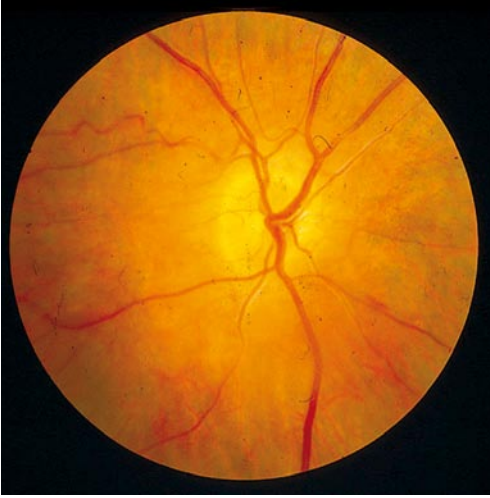
A more aggressive assessment should be considered when atypical features of optic neuritis are present. Interestingly, in the ONTT, some specific ocular findings were associated with a 0% chance of developing MS within 10 years in the patients with a normal baseline MRI, including absence of light perception in the affected eye, absence of pain, severe optic disc edema, peripapillary hemorrhage, and retinal exudates (Table 1.6; Fig. 1.1). These findings emphasize the importance of a dilated funduscopy examination by an ophthalmologist for all patients with

**Table 1.6.** Features not associated with subsequent development of MS in the ONTT patients who had a normal baseline MRI. In the group of 191 patients with optic neuritis and a normal baseline MRI, none of the patients with at least one of the following characteristics subsequently developed clinically definite MS at the 10-year follow-up

|   | Number of patients (n=191) |
|---|----------------------------|
| Absence of light perception in the affected eye | 6                          |
| Absence of periocular pain                      | 18                         |
| Severe optic disc edema                         | 22                         |
| Peripapillary hemorrhage                        | 16                         |
| Retinal exudates                                | 8                          |

acute optic neuritis, as these findings should help identify a group of patients with very low risk of MS [49, 51, 54].

Brain MRI (including fluid attenuated inversion recovery or FLAIR images and administration of contrast) is essential to evaluate the risk of MS, and it may be repeated over time [55] (Fig. 1.2). Spinal cord imaging is usually not helpful in patients with clinically isolated optic neuritis [20]. Dedicated orbital views (thin sec-



**Fig. 1.1.** Funduscopy examination of a patient with acute painful visual loss related to an optic neuropathy. The optic nerve is very swollen and there are peripapillary hemorrhages. The optic neuritis was related to syphilis

tions with fat suppression, and administration of contrast) are only necessary in atypical optic neuritis, as the documentation of optic nerve enhancement, although very common, is not necessary in most cases of typical acute optic neuritis [28, 57].

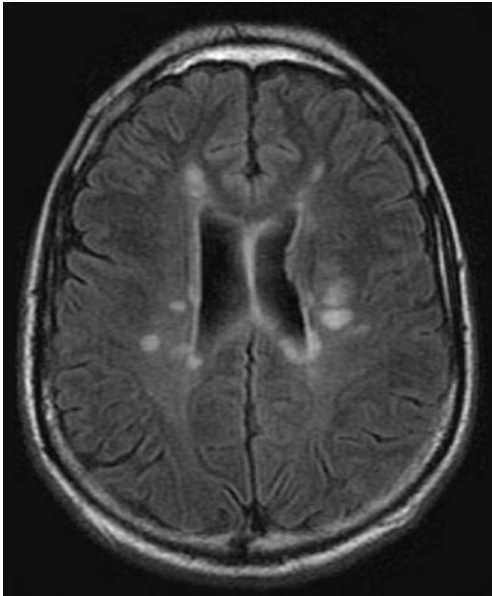
Lumbar puncture for cerebrospinal fluid (CSF) analysis is usually not necessary in patients with typical acute optic neuritis. Although CSF oligoclonal IgG bands, IgG index, and intrathecal IgG synthesis are included in the diagnostic criteria of MS, they are not specific for MS [25]. In the ONTT, CSF studies showed that only the presence of oligoclonal bands (in 50% of patients) correlated with later development of MS, but these patients also had abnormal baseline MRI, already predicting a higher risk of MS. There was no additional value of CSF evaluation [17, 30, 65, 66]. A recent study suggested that the presence of oligoclonal bands in the CSF of patients with a clinically isolated syndrome and abnormal MRI was highly specific and sensitive for early prediction of conversion to MS; however, very few patients had isolated optic neuritis in the study [38].

## Summary for the Clinician

- Laboratory tests are usually only obtained to rule out an underlying disorder when the clinical presentation is not typical of acute idiopathic optic neuritis.
- Dilated funduscopy examination of all optic neuritis patients is essential to identify features that would place certain patients with a normal baseline MRI in a low-risk subgroup for development of subsequent MS (Table 1.6).
- Follow-up should demonstrate spontaneous improvement of visual function within a few weeks in >90% of cases and the absence of improvement should raise concern about another diagnosis.
- Lumbar puncture should only be performed in select atypical cases of optic neuritis, especially in bilateral cases, in childhood, or when an infectious or systemic inflammatory disorder is suspected [57].
- Brain MRI is essential for all optic neuritis patients, and this has become the standard of care to evaluate the risk of MS.

### 1.3.2 Acute Therapeutic Options

Acute treatment options for acute idiopathic optic neuritis include intravenous methylprednisolone or observation alone. Intravenous methylprednisolone hastens visual recovery, but has no effect on the final visual outcome. In patients with abnormal baseline MRI, treatment with intravenous steroids may delay the onset of MS within the first 2 years following an episode of optic neuritis [7]. Intravenous methylprednisolone as used in the ONTT is generally well tolerated, but mild steroid-related side-effects are common, including insomnia, weight gain, and mood alteration [7]. As emphasized by the American Academy of Neurology (AAN) practice parameter statement [33], oral prednisone in conventional doses of 1 mg/kg per day should not be used in the treatment of idiopathic acute



**Fig. 1.2.** Axial brain MRI (FLAIR sequence) demonstrating hypersignals in the periventricular white matter

optic neuritis. It is unclear whether high-dose oral corticosteroids would also increase the risk of recurrent optic neuritis [33]. A small prospective controlled clinical trial of oral methylprednisolone (500 mg every day for 5 days) showed no increased rate of demyelinating attacks [67]. Some centers now routinely use high-dose oral prednisone (1250 mg) once daily for 3–5 days; however, supportive evidence is lacking, and no trial comparing intravenous high-dose (1000 mg per day) to oral high-dose (1250 mg per day) has been done.

Intravenous immunoglobulin (IVIG) may attenuate clinical and MRI-identified disease activity in patients with relapsing–remitting MS [1, 36, 69]; however, a randomized trial of IVIG treatment in acute optic neuritis concluded that there was no effect of IVIG on long-term visual function or preservation of optic nerve axonal function [64].

### Summary for the Clinician

- Oral corticosteroids in conventional doses of 1 mg/kg per day may increase the risk of recurrence, and should *not* be used in the treatment of acute idiopathic optic neuritis.
- Intravenous methylprednisolone hastens visual recovery, but has no effect on the final visual outcome.
- The decision to use intravenous methylprednisolone should be individualized and should be made after discussing the risks and benefits of this therapy with the patient.
- No treatment is a reasonable alternative, as steroids do not change the long-term prognosis of patients with optic neuritis.

### 1.3.3 Chronic Therapeutic Options

Recent pathological and MRI studies have suggested that axonal damage occurs early during the course of MS [2, 10, 21, 23, 41, 44, 58]. It has been emphasized that, once axonal damage occurs, it may result in permanent neurological deficits. The issue of axonal damage and gray matter atrophy is at the center of the ongoing debate over whether to intervene early with immunomodulatory agents in patients with clinically isolated syndromes [4, 27], especially those predicted to be at high risk for the subsequent development of MS. Results of the CHAMPS [16] ETOMS [18], and BENEFIT [26, 56] studies suggest that patients with optic neuritis and abnormal baseline MRI (“high-risk patients”) should be considered for interferon beta therapy. The CHAMPIONS study [15] even suggested that such treatment should be initiated early after the first occurrence of optic neuritis. A trial to assess the effect of glatiramer acetate in monosymptomatic patients has been initiated.

Some authors advocate immediate treatment to avoid any further axonal injury, while others suggest delaying long-term treatment, and repeating the MRI to prove the dissemination of lesions in space and time prior to initiating such a

serious and costly treatment. This topic remains debated and recommendations vary among countries [44].

IVIG has also been suggested to facilitate recovery in chronic optic neuritis [61, 62, 63, 72, 73]; however, IVIG administration does not significantly reverse persistent visual loss [48].

### Summary for the Clinician

- Evidence from recent randomized, placebo-controlled trials supports early intervention with immunomodulatory agents in high-risk patients with clinically isolated syndromes to decrease the risk of subsequent development of MS [4, 28].
- The decision to treat high-risk optic neuritis patients with immunomodulatory agents should be individualized.

## 1.4 Pediatric Optic Neuritis

The natural history and management of optic neuritis in children is different than in adults [11]. The data on pediatric optic neuritis are scarce and controversial, and are primarily based on small retrospective chart reviews [12, 45], and on one longitudinal study [37]. These limited studies suggest:

- Mean age of onset: around 10 years
- 2/3 female
- 2/3 have disc edema (compared to 1/3 of adults)
- 2/3 have bilateral involvement
- 2/3 have a history of a preceding febrile illness within 2 weeks of onset
- Those with unilateral involvement may have a greater tendency to develop subsequent MS, but also carry a better visual prognosis than those with bilateral involvement
- Subsequent development of MS is less than in adults, and those who do develop MS are older (mean age 12 years) at the onset of optic neuritis

### Summary for the Clinician

- In children, data are lacking regarding both the effects of intravenous methylprednisolone on visual recovery and the effects of immunomodulatory agents on the subsequent development of MS.
- Based on the studies done in adults, it would seem reasonable to offer IV steroids in cases with severe visual loss (especially when bilateral), and to consider immunomodulatory agents when the brain MRI is abnormal [4].

### References

1. Achiron A, Kishner I, Sarova-Pinhas I et al (2004) Intravenous immunoglobulin treatment following the first demyelinating event suggestive of multiple sclerosis: a randomized, double-blind, placebo-controlled trial. *Arch Neurol* 61:1515–1520
2. Arnold AC (2005) Evolving management of optic neuritis and multiple sclerosis. *Am J Ophthalmol* 139:1101–1108
3. Atkins EJ, Bioussé V, Newman NJ (2006) The natural history of optic neuritis. *Rev Neurol Dis* 3:45–55
4. Balcer L (2006) Optic neuritis. *New Engl J Med* 354:1273–1280
5. Barkhof F, Filippi M, Miller DH et al (1997) Isolated demyelinating syndromes: comparison of different magnetic resonance imaging criteria to predict conversion to clinically definite multiple sclerosis. *Brain* 120:2059–2069
6. Beck RW, Cleary PA, Anderson MM Jr. et al (1992) A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. *N Engl J Med* 326:581–588
7. Beck RW, Cleary PA, Trobe JD et al (1993) The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. *N Engl J Med* 329:1764–1769
8. Beck RW, Arrington J, Murtagh FR et al (1993) Brain MRI in acute optic neuritis: experience of the Optic Neuritis Study Group. *Arch Neurol* 8:841–846

9. Beck RW, Chandler DL, Cole SR et al (2002) Interferon  $\beta$ -1a for early multiple sclerosis: CHAMPS trial subgroup analyses. *Ann Neurol* 51:481–490
10. Bermel R, Puli S, Rudick R et al (2005) Gray matter MRI T2 hypointensity predicts longitudinal atrophy in multiple sclerosis. *Arch Neurol* 62:1371–1376
11. Boomer JA, Siatkowski RM (2003) Optic neuritis in adults and children. *Semin Ophthalmol* 18:174–180
12. Brady KM, Brar AS, Lee AG et al (1999) Optic neuritis in children: clinical features and visual outcome. *J AAPOS* 3:98–103
13. Brex P, Ciccarelli O, O’Riordan J et al (2002) A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. *N Engl J Med* 346:156–164
14. Brusaferrri F, Candelise F (2000) Steroids for multiple sclerosis and optic neuritis: a meta-analysis of randomized controlled clinical trials. *J Neurol* 247:435–442
15. CHAMPIONS Study Group (2006) IM interferon  $\beta$ -1a delays definite multiple sclerosis 5 years after a first demyelinating event. *Neurology* 66:678–684
16. CHAMPS Study Group (2001) Interferon  $\beta$ -1a for optic neuritis patients at high-risk for multiple sclerosis. *Am J Ophthalmol* 132:463–471
17. Cole SR, Beck RW, Moke PS et al (1998) The predictive value of CSF oligoclonal banding for MS 5 years after optic neuritis. *Neurology* 51:885–887
18. Comi C, Filippi M, Barkhof F et al (2001) Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomized study (ETOMS). *Lancet* 358:1586–1582
19. Dalton CM, Brex PA, Miszkil KA et al (2003) New T2 lesions enable an earlier diagnosis of multiple sclerosis in clinically isolated syndromes. *Ann Neurol* 53:673–676
20. Dalton CM, Brex PA, Miszkil KA et al (2003) Spinal cord MRI in clinically isolated optic neuritis. *J Neurol Neurosurg Psychiatry* 74:1587–1580
21. De Stefano N, Narayanan S, Francis GS et al (2001) Evidence of axonal damage in the early stages of multiple sclerosis and its relevance to disability. *Arch Neurol* 58:65–70
22. Ebers GC (1985) Optic neuritis and multiple sclerosis. *Arch Neurol* 42:702–704
23. Filippi M, Tortorella C, Rovaris M et al (2000) Changes in the normal appearing brain tissue and cognitive impairment in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 68:156–161
24. Francis DA, Compston DA, Batchelor JR, McDonald WI (1987) A reassessment of the risk of multiple sclerosis developing in patients with optic neuritis after extended follow-up. *J Neurol Neurosurg Psychiatry* 50:758–765
25. Frederiksen JL (1998) Can CSF predict the course of optic neuritis? *Mult Scler* 4:132–135
26. Freedman M, Kappos L, Polman C et al (2006) Betaseron in newly emerging multiple sclerosis for initial treatment (BENEFIT): clinical outcomes. *Neurology* 66:S02.001
27. Frohman E, Racke M (2000) To treat or not to treat? The therapeutic dilemma of idiopathic monosymptomatic demyelinating syndromes. *Arch Neurol* 58:930–932
28. Frohman E, Frohman T, Zee D et al (2005) The neuro-ophthalmology of multiple sclerosis. *Lancet Neurol* 4:111–121
29. Ghezzi A, Martinelli V, Torri V et al (1999) Long-term follow-up of isolated optic neuritis: the risk of developing multiple sclerosis, its outcome, and the prognostic role of paraclinical tests. *J Neurol* 246:770–775
30. Jacobs LD, Kaba SE, Miller CM et al (1997) Correlation of clinical, MRI and CSF findings in optic neuritis. *Ann Neurol* 41:392–398
31. Jacobs LD, Beck RW, Simon JH et al (2000) The effect of intramuscular interferon beta 1a treatment initiated at the time of a first acute clinical demyelinating event on the rate of development of clinically definite multiple sclerosis. *N Engl J Med* 343:898–904
32. Jin YP, de Pedro-Cuesta J, Huang YH, Söderström M (2003) Predicting multiple sclerosis at optic neuritis onset. *Mult Scler* 9:135–141
33. Kaufman DI, Trobe JD, Eggenberger ER et al (2000) Practice parameter: the role of corticosteroids in the management of acute monosymptomatic optic neuritis. *Neurology* 54:2039–2044
34. Korteweg T, Tintoré M, Uidehaag B et al (2006) MRI criteria for dissemination in space in patients with clinically isolated syndromes: a multicentre follow-up study. *Lancet Neurol* 5:221–227
35. Kurtzke JF (1985) Optic neuritis or multiple sclerosis. *Arch Neurol* 42:704–710



36. Lewanska M, Siger-Zajdel M, Selmaj K (2002) No difference in efficacy of two different doses of intravenous immunoglobulins in MS: clinical and MRI assessment. *Eur J Neurol* 9:565–582
37. Lucchinetti CF, Kiers L, O'Duffy A et al (1997) Risk factors for developing multiple sclerosis after childhood optic neuritis. *Neurology* 49:1413–1418
38. Masjuan J, Alvarez-Cermeno JC, Garcia-Barragan N et al (2006) Clinically isolated syndromes. A new oligoclonal band test accurately predicts conversion to MS. *Neurology* 66:586–588
39. McDonald W, Compston A, Edam G et al (2001) Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. *Ann Neurol* 50:121–127
40. Miller DH, Ormerod IEC, McDonald WI et al (1988) The early risk of multiple sclerosis after optic neuritis. *J Neurol Neurosurg Psychiatry* 51:1569–1581
41. Miller D, Barkhof F, Montalban X et al (2005) Clinically isolated syndromes suggestive of multiple sclerosis, part I: natural history, pathogenesis, diagnosis, and prognosis. *Lancet Neurol* 4:281–288
42. Miller D, Barkhof F, Montalban X et al (2005) Clinically isolated syndromes suggestive of multiple sclerosis, part II: non-conventional MRI, recovery processes, and management. *Lancet Neurol* 4:341–348
43. Minneboo A, Barkhof F, Polman CH et al (2004) Infratentorial lesions predict long-term disability in patients with initial findings suggestive of multiple sclerosis. *Arch Neurol* 61:217–221
44. Montalban X (2004) The pros and cons of early treatment of relapsing forms of multiple sclerosis. *J Neurol* 251 [Suppl. 4]: IV/30–IV/34
45. Morales DS, Siatkowski RM, Howard CW, Warman R (2000) Optic neuritis in children. *J Pediatr Ophthalmol Strabismus* 37:254–259
46. Morrissey SP, Miller DH, Kendall BE et al (1993) The significance of brain magnetic resonance imaging abnormalities at presentation with clinically isolated syndromes suggestive of multiple sclerosis. A 5-year follow-up study. *Brain* 116:135–146
47. Nillson P, Larsson EM, Maly-Sundgren P et al (2005) Predicting the outcome of optic neuritis – evaluation of risk factors after 30 years of follow-up. *J Neurol* 252:396–402
48. Noseworthy JH, O'Brien PC, Petterson TM et al (2001) A randomized trial of intravenous immunoglobulin in inflammatory demyelinating optic neuritis. *Neurology* 56:1514–1522
49. Optic Neuritis Study Group (1997) The 5 year risk of MS after optic neuritis: experience of the optic neuritis treatment trial. *Neurology* 49:1404–1413
50. Optic Neuritis Study Group (1997) Visual function 5 years after optic neuritis. *Arch Ophthalmol* 115:1545–1552
51. Optic Neuritis Study Group (2003) High risk and low risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the Optic Neuritis Treatment Trial. *Arch Ophthalmol* 121:944–949
52. Optic Neuritis Study Group (2004) Visual function more than 10 years after optic neuritis: experience of the Optic Neuritis Treatment Trial. *Am J Ophthalmol* 137:77–83
53. Optic Neuritis Study Group (2004) Neurologic impairment after optic neuritis. *Arch Neurol* 61:1386–1389
54. Optic Neuritis Study Group (2004) Long-term magnetic resonance imaging changes after optic neuritis in patients without clinically definite multiple sclerosis. *Arch Neurol* 61:1538–1541
55. Polman CH, Reingold SC, Edan G et al (2005) Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald” criteria. *Ann Neurol* 58:840–846
56. Polman C, Kappos L, Freedman M et al (2006) Betaseron in newly emerging multiple sclerosis for initial treatment (BENEFIT): subgroup analyses. *Neurology* 66:S02.002
57. Purvin V (2000) Optic neuropathies for the neurologist. *Semin Neurol* 20:97–110
58. Revesz T (2000) Axonal lesions in MS: an old story revisited. *Brain* 123:203–204
59. Rizzo JF, Lessell S (1991) Optic neuritis and ischemic optic neuropathy. Overlapping clinical profiles. *Arch Ophthalmol* 109:1668–1672
60. Rizzo J, Lessell S (1998) Risk of developing multiple sclerosis after uncomplicated optic neuritis: a long term prospective study. *Neurology* 38:185–190
61. Rodriguez M, Lennon VA (1990) Immunoglobulins promote remyelination in the central nervous system. *Ann Neurol* 27:12–17

62. Rodriguez M, Miller DJ (1994) Immune promotion of central nervous system remyelination. *Prog Brain Res* 103:343–355
63. Rodriguez M, Miller DJ, Lennon VA (1996) Immunoglobulins reactive with myelin basic protein promote CNS remyelination. *Neurology* 46:538–545
64. Roed HG, Langkilde A, Sellebjerg F et al (2005) A double-blind, randomized trial of IV immunoglobulin treatment in acute optic neuritis. *Neurology* 65:804–810
65. Rolak LA, Beck RW, Paty DW et al (1996) Cerebrospinal fluid in acute optic neuritis: experience of the optic neuritis treatment trial. *Neurology* 46:368–372
66. Sandberg-Wolheim M, Bynke H, Cronqvist S et al (1990) A long term prospective study of optic neuritis: evaluation of risk factors. *Ann Neurol* 27:386–393
67. Sellebjerg F, Nielsen HS, Frederiksen JL et al (1999) A randomized, controlled trial of oral high-dose methylprednisolone in acute optic neuritis. *Neurology* 52:1479–1484
68. Söderström M, Jin YP, Hillert J, Link H (1998) Optic neuritis, prognosis for multiple sclerosis from MRI, CSF, and HLA findings. *Neurology* 50:708–714
69. Sorensen PS, Wanscher B, Jensen CV et al (1998) Intravenous immunoglobulin G reduces MRI activity in relapsing multiple sclerosis. *Neurology* 50:1273–1281
70. Tintoré M, Rovira A, Martinez MJ et al (2000) Isolated demyelinating syndromes: comparison of different diagnostic MRI criteria to predict conversion to clinically definite multiple sclerosis. *Am J Neuroradiol* 21:702–706
71. Tintoré M, Rovira A, Rio J et al (2005) Is optic neuritis more benign than other first attacks in multiple sclerosis? *Ann Neurol* 57:210–215
72. Van Engelen BG, Hommes OR, Pinckers A et al (1992) Improved vision after intravenous immunoglobulin in stable demyelinating optic neuritis. *Ann Neurol* 32:834–835
73. Van Engelen BG, Miller DJ, Pavelko KD et al (1994) Promotion of remyelination by polyclonal immunoglobulin and IVIg in Theiler's virus induced demyelination and in MS. *J Neurol Neurosurg Psychiatry* 58 [Suppl. 1]:65–68
74. Weinshenker BG, Bass B, Rice GP et al (1989) The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain* 112:133–146