# **Contents**

# xv Preface to the Third, Revised and Expanded Edition

Wiersinga, W.M. (Amsterdam); Kahaly, G.J. (Mainz)

## **XVI Preface to the Second, Revised Edition**

Wiersinga, W.M. (Amsterdam); Kahaly, G.J. (Mainz)

#### **XVI** Preface to the First Edition

Wiersinga, W.M. (Amsterdam); Kahaly, G.J. (Mainz)

### Diagnosis and Pathogenesis

#### 1 Clinical Manifestations

Dickinson, A.J. (Newcastle upon Tyne); Hintschich, C. (Munich)

- 1 What Are the Common Signs and Symptoms of Early Graves' Orbitopathy?
- 1 What Are Other Signs and Symptoms of Graves' Orbitopathy?
- 3 What Signs Should Question the Diagnosis of Graves' Orbitopathy?
- 3 Are There Racial Differences in How Graves' Orbitopathy Manifests?
- 4 Is the Presentation of Graves' Orbitopathy Different in Older Compared to Younger Patients?
- 4 Why Can the Clinical Presentation of Graves' Orbitopathy Be So Variable?
- 5 Can You Give Me a Short Mechanistic Explanation for All These Clinical Manifestations?
- 6 What Do the Terms "Activity" and "Severity" Denote?
- 7 Why Is It Important to Distinguish Activity and Severity when Evaluating Patients?
- 7 What Signs and Symptoms Are Valuable for Assessing Activity?
- 7 How Are These Signs Assessed?
- 10 How Reproducible Are These Assessments?
- 11 What Value Does the "Clinical Activity Score" Have?
- 11 Do Patients without Signs of Activity Ever Have Active Disease?
- 12 What Should I Do if I Am Not Sure whether the Disease Is Active?
- 12 Are There Any Other Ways to Evaluate Activity other than Clinical Examination?
- 13 When Should These Other Methods for Assessing Activity Be Used in Routine Clinical Practice?
- 14 What Signs Are Helpful for Assessing Severity?
- 14 What Value Does the Mnemonic "NOSPECS" Have?
- 14 How Are Signs of Severity Assessed?
- 18 How Reproducible Are These Assessments?
- 19 How Is Severity Best Classified?
- 19 How Do You Decide whether a Patient Has Dysthyroid Optic Neuropathy?
- 21 Can Dysthyroid Optic Neuropathy Ever Be Present with Normal Vision?
- 21 Are Some Patients at Particular Risk?
- 21 What Other Assessments Are Useful in Evaluating Possible Dysthyroid Optic Neuropathy?
- 22 Should These Tests Be Performed in All Patients at Every Assessment?
- 22 Are There Any Other Assessment Systems in Common Use?
- 23 References



# 26 Orbit-Thyroid Relationship

Marinò, M. (Pisa)

- 26 Should This Condition Always Be Called Graves' Orbitopathy?
- 26 Is Graves' Orbitopathy Exclusively Occurring in Patients with Graves' Hyperthyroidism?
- 28 Do All Patients with Graves' Hyperthyroidism Have Graves' Orbitopathy?
- 28 Are There Any Relationships between Hyperthyroidism, Hypothyroidism, and Graves' Orbitopathy?
- 29 Is Graves' Orbitopathy Related to Thyroid Autoimmunity?
- 29 Are There Other Extrathyroidal Manifestations of Graves' Disease apart from Graves' Orbitopathy?
- 31 References

#### 33 Epidemiology

Burlacu, M.-C.: Daumerie, C. (Brussels)

- 33 What Is the Estimated Incidence and Prevalence of Graves' Orbitopathy?
- 34 Has the Occurrence of Graves' Orbitopathy Changed over the Last Few Decades?
- 35 Is the Age and Sex Distribution of Graves' Orbitopathy Similar to That of Graves' Hyperthyroidism?
- 36 Are There Ethnic Differences?
- 36 What Are the Risk Factors for the Occurrence of Graves' Orbitopathy?
- 37 Can Particular Drugs Trigger or Modify Graves' Orbitopathy and Its Course?
- 38 Is Tobacco Bad for Graves' Orbitopathy?
- 38 Has Nutrition an Effect on Graves' Orbitopathy?
- 38 Does Total Thyroidectomy for Other Diseases than Graves' Disease Preclude the Development of Graves' Orbitopathy?
- 39 References

## 41 Pathogenesis

Salvi, M. (Milan); Berchner-Pfannschmidt, U. (Essen); Ludgate, M. (Cardiff)

- 41 What Are the Pathological Changes in Orbital Tissue in Graves' Orbitopathy?
- 43 How Do the Pathological Changes Give Rise to the Clinical Manifestations?
- 44 What Triggers Graves' Orbitopathy?
- 45 Is Graves' Orbitopathy Triggered by an Autoimmune Phenomenon? If So, What Is the Nature of the Autoantigen?
- 47 Why Is the Orbit Special and a Target for Thyroid Autoimmunity?
- 48 What Kind of Immune Reactions Take Place within the Orbit?
- 50 Does Thyroid-Stimulating Hormone Receptor Activation and/or Autoreactivity to Thyroid-Stimulating Hormone Receptor Play a Role in the Onset or Development of Graves' Orbitopathy?
- 52 Is There a Familial Predisposition or a Specific Genetic Background for Graves' Orbitopathy?
- 53 How Do Environmental Factors Increase the Risk and Severity of Graves' Orbitopathy?
- 54 How May These Observations and Current Understanding Lead to More Effective Treatment of Graves' Orbitopathy?
- 56 References

# 61 Orbital Imaging

Pitz, S.; Müller-Forell, W. (Mainz)

- 61 Is Orbital Imaging Always Necessary?
- 61 What Are the Relative Benefits of Orbital CT and MRI?
- 65 What Is Apical Crowding?
- 68 What Is the Place of Orbital Ultrasound?
- 70 What Lessons Can We Learn from Orbital Octreoscan?
- 70 What Other Imaging Techniques May Be Useful?
- 71 References

# 74 Diagnosis and Differential Diagnosis of Graves' Orbitopathy

Konuk, O. (Ankara); Anagnostis, P. (Thessaloniki)

- 74 Can You Give an Overall Scheme for the Diagnosis of Graves' Orbitopathy?
- 75 Which Clinical Findings Are Helpful in Making a Diagnosis of Graves' Orbitopathy?
- 81 Can One Make a Diagnosis of Graves' Orbitopathy Based on Medical History and Clinical Picture Alone?
- 82 Do We Always Need to Order Thyroid Autoantibody and Thyroid Function Tests?
- 83 Which Imaging Technique Is Best to Make a Diagnosis of Graves' Orbitopathy, and Is Imaging Always Requested?
- 84 Which Are the Most Frequent Conditions Mimicking Graves' Orbitopathy?
- 91 References

# 93 Natural History

Mamoojee, Y.; Pearce, S.H.S. (Newcastle upon Tyne)

- 93 Does Graves' Orbitopathy Occur at the Same Time as Hyperthyroidism?
- 94 Does Restoring Euthyroidism Lead to Improvement in Graves' Orbitopathy?
- 95 What Effect May Hypothyroidism Have?
- 95 What Is the Typical Course of the Disease?
- 96 What Happens to Orbital Fat during the Course of the Disease?
- 97 What Is the Difference between Activity and Severity?
- 99 How Do You Determine Which Phase of the Disease the Patient Is Displaying?
- 99 How Does the Phase of the Disease Influence the Choice of Treatment?
- 100 Will Graves' Orbitopathy Eventually Burn Itself Out?
- 100 Will the Orbital Changes Return to Normal when the Condition Eventually Resolves?
- 100 How Long Is It Likely to Take before the Disease Becomes Inactive?
- 101 Once the Condition Has Become Inactive (whether Treated or Untreated), Is It Likely to Flare Up Again?
- 101 Are There Any Other Factors, Additional to Thyroid Status, That May Influence the Course of the Disease?
- 102 References

# Management

# 105 General Management Plan for Graves' Orbitopathy

Bartalena, L. (Varese)

- 105 Is There General Agreement among Specialists on How to Manage Graves' Orbitopathy?
- 105 What Are the Priorities when Faced with a New Presentation of Graves' Orbitopathy?
- 107 Should the Patient Be Informed about Risk Factors Affecting the Course of Graves' Orbitopathy?
- 108 What Is the Evidence about the Role of Smoking on the Course of Graves' Orbitopathy?
- 109 Does Thyroid Status Affect Graves' Orbitopathy?
- 109 Are There Simple Measures That Can Help the Eyes?
- 110 Is Early Referral to Specialized Centres Important?
- 111 Can You Provide the Patient with an Overall Management Scheme?
- 111 References

### 113 Combined Thyroid-Eye Clinics

Törüner, F.B.; Konuk, O.; Ayvaz, G. (Ankara)

- 113 What Are Combined Thyroid-Eye Clinics?
- 115 Why Is a Multidisciplinary Approach Recommended?

- 115 Can Patient Support Groups Be Helpful?
- 117 I Have Heard of a Fast-Track Clinic for Graves' Orbitopathy Patients: What Is That?
- 117 What Can I Expect when Starting a Combined Thyroid-Eye Clinic?
- 117 References

# 119 Thyroid Treatment

Hegedüs, L.; Brix, T.H. (Odense)

- 120 Do the Eyes Care How Euthyroidism Is Obtained and Maintained?
- 123 Are There Criteria for Preferring One of the Treatment Options for Hyperthyroidism over the Others in Graves' Orbitopathy?
- 124 Can Risk Factors Which Predict Appearance or Worsening of Graves' Orbitopathy after Radioiodine Be Identified?
- 125 Should the Presence of Graves' Orbitopathy Restrict Our Use of Radioiodine Therapy?
- 126 Does Avoiding Transient Hypothyroidism following Radioiodine Therapy Affect the Course of Graves' Orbitopathy?
- 127 What Is the Role of Total Thyroid Ablation in the Management of Hyperthyroidism in Graves' Orbitopathy?
- 128 Conclusions
- 128 References

# 131 Management of Mild Graves' Orbitopathy

Marcocci, C.; Rocchi, R. (Pisa)

- 131 Which Parameters Should Be Taken into Account to Define a Clinically Evident Graves' Orbitopathy as Mild?
- 132 Are Mild Forms Likely to Progress to More Severe Graves' Orbitopathy?
- 133 Is a "Wait-and-See" Policy Justified in Patients with Mild Graves' Orbitopathy?
- 134 Are Low-Dosage Oral Steroids Advisable or Is Orbital Radiotherapy Preferable?
- 135 What Is the Rationale for Antioxidant Therapy like Selenium in Graves' Orbitopathy?
- 138 References

# 140 Management of Moderately Severe Graves' Orbitopathy

Kahaly, G.J. (Mainz)

- 140 How Is Moderately Severe Graves' Orbitopathy Defined?
- 140 Is Immunosuppression Indicated in Moderately Severe Graves' Orbitopathy?
- 141 What Are the Cellular and Molecular Mechanisms of Steroid Anti-Inflammation and Immunosuppression?
- 145 What Are the Results of Randomized Trials with Steroids?
- 155 What Are the Results of Randomized Trials Using Orbital Radiotherapy?
- 159 Do You Favour Combined Steroid/Radiotherapy?
- 160 What Are the Results of Randomized Trials Using Non-Steroid Immunosuppressants?
- 165 What Are the Results of Randomized Trials Using Somatostatin Analogues?
- 167 How Should a Diabetic or Hypertensive Patient with Moderately Severe Graves' Orbitopathy Be Treated?
- 168 What Should You Do if Steroids Fail?
- 168 What Is the Optimal Thyroid Treatment in Patients with Graves' Hyperthyroidism and Moderately Severe Active Graves' Orbitopathy?
- 169 What Are the Actual Evidence-Based Therapeutic Recommendations for Patients with Moderately Severe Graves' Orbitopathy?
- 169 What Were the Recommendations of the EUGOGO Consensus Statement for the Management of Moderately Severe Graves' Orbitopathy?

- 170 What Do the ETA/EUGOGO Guidelines for the Management of Graves' Orbitopathy Recommend?
- 171 Acknowledgements
- 171 References

### 177 Novel Immunomodulatory Treatment Modalities

Lane, L.C.; Perros, P.; Pearce, S.H.S. (Newcastle upon Tyne)

- 177 Why Look for New Immunomodulatory Treatments?
- 177 What Are the Targets for Potential Novel Therapies?
- 179 Rituximab
- 184 What Are the Most Likely Targets for Therapeutic Intervention?
- 189 Should Clinicians Be Cautious about Trying Novel Immunomodulators?
- 190 References

# 193 Management of Very Severe Graves' Orbitopathy: Dysthyroid Optic Neuropathy and Corneal Breakdown

Boschi, A. (Brussels); Currò, N. (Milan)

- 193 How Do You Define Dysthyroid Optic Neuropathy? What Is the Causative Mechanism?
- 194 Are There Specific Risk Factors for Dysthyroid Optic Neuropathy?
- 195 Which Symptoms Should Alert Me for Dysthyroid Optic Neuropathy?
- 196 What Are the Ophthalmological Signs of Dysthyroid Optic Neuropathy?
- 196 Are Additional Investigations Helpful?
- 197 How Fast Can Dysthyroid Optic Neuropathy Progress? Is Urgent Treatment Necessary?
- 197 What Is the Evidence Base for the Treatment of Dysthyroid Optic Neuropathy?
- 198 Are Predictive Factors for Response to Steroid Treatment in Dysthyroid Optic Neuropathy Patients Well Defined?
- 199 What Is the Role of Surgery in Dysthyroid Optic Neuropathy?
- 199 How Many Patients Become Blind due to Dysthyroid Optic Neuropathy?
- 199 How Can I Recognize Corneal Breakdown?
- 200 What Is the Recommended Treatment of Corneal Breakdown?
- 200 References

#### 202 Local Treatment Modalities

Boboridis, K.; Anagnostis, P. (Thessaloniki)

- 202 Is Graves' Orbitopathy Related to Ocular Surface Pathology?
- 202 When and How Should We Support the Ocular Surface?
- 204 Can Local Measures Address Eyelid Retraction?
- 204 Can Local Measures Reduce Orbital Inflammation in Graves' Orbitopathy?
- 205 Can Local Measures Improve the Visual Disturbance and Diplopia?
- 205 References

# 207 Rehabilitative Surgery

Baldeschi, L. (Brussels)

- 207 Why Is This Chapter Called Rehabilitative Surgery and Not Cosmetic Surgery?
- 208 What Are the Steps and Timing of Rehabilitative Surgery?
- 209 How Should Patients Be Selected for Rehabilitative Surgery?
- 210 References

# 211 Orbital Decompression

Baldeschi, L. (Brussels); Morris, D.S. (Cardiff)

- 211 What Is Orbital Decompression?
- 211 What Are the Aims of Orbital Decompression?
- 215 What Are the Different Types of Orbital Decompression?
- 223 What Are the Possible Complications of Orbital Decompression?
- 224 Can Complications Be Predicted or Prevented?
- 225 Are Technical Developments in Decompression Surgery and Other Surgical Rehabilitative Procedures for Graves' Orbitopathy to Be Expected?
- 226 Are Conceptual Developments in Decompression Surgery and Other Surgical Rehabilitative Procedures for Graves' Orbitopathy to Be Expected?
- 227 References

# 230 Eye Muscle Surgery

Nardi, M. (Pisa); Eckstein, A. (Essen)

- 230 What Are the Reasons for Impairment of Ocular Motility in Graves' Orbitopathy?
- 230 Which Muscles Are Involved?
- 231 How Does Decompression Influence Ocular Motility?
- 232 How Do You Identify the Affected Muscles?
- 234 How Can You Avoid Diagnostic Errors in Complex Cases?
- 236 What Is the Optimal Pretreatment before You Start Eye Muscle Surgery?
- 236 When Is the Right Time for Surgery?
- 236 How Do You Deal with Diplopia until Surgery Is Possible?
- 237 How Can You Evaluate the Need for Surgery?
- 238 The Surgical Plan: What Procedures Are Recommended?
- 241 What Are the Possible Complications of Surgery and How Can I Avoid or Manage Them?
- 243 What Can You Realistically Expect from Surgery?
- 243 How Can Success of Surgery Be Measured?
- 244 How Should You Advise the Patient?
- 244 References

### 247 Eyelid Surgery

Clarke, L. (Newcastle upon Tyne); Eckstein, A. (Essen)

- 247 What Are the Indications for Eyelid Surgery in Patients with Graves' Orbitopathy?
- 248 Is Botulinum Toxin Useful?
- 249 Is Surgical Intervention Indicated in Corneal Ulceration Secondary to Exposure Keratopathy?
- 250 Does Orbital Decompression Have Any Effect on Lid Retraction?
- 250 Does Squint Surgery Influence the Lid Configuration?
- 251 Can Decompression Be Combined with Lid Lengthening?
- 252 What Surgical Procedures Are Available for Correction of Upper Lid Retraction?
- 254 Are There Complications?
- 254 What Surgical Procedures Are Available for Correction of Lower Lid Retraction?
- 255 Should This Be Combined with Horizontal Lid Tightening?
- 256 Which Materials Are Suitable for Use as Spacers? Should the Use of Allogeneic Grafts Be Avoided?
- 257 Are There Complications?
- 257 What about Upper Lid Debulking and Upper and Lower Lid Blepharoplasty?
- 257 Does Lid Surgery Improve the Quality of Life of the Patients?
- 257 How Can the Effect of Lid Surgery Be Quantified?
- 258 References

#### Miscellaneous Issues

### 260 Quality of Life

Wiersinga, W.M. (Amsterdam)

- 260 What Is Quality of Life?
- 260 What Is the Usefulness of Quality of Life Measurements?
- 262 What Is Known about General Health-Related Quality of Life in Graves' Orbitopathy?
- 263 Is There a Graves' Orbitopathy-Specific Quality of Life Questionnaire?
- 265 What Are the Results of the GO-QoL?
- 265 Can You Explain Response Shift in Quality of Life?
- 266 Can GO-QoL Be Used as a Separate Outcome Measurement in Graves' Orbitopathy?
- 267 What Is the Experience with GO-QoL as Outcome Measurement in the Literature?
- 268 Are There Other Disease-Specific Quality of Life Questionnaires for Graves' Orbitopathy?
- 270 Are There Qualitative Studies on Quality of Life in Graves' Orbitopathy?
- 270 Is Quality of Life Fully Restored after Treatment of Graves' Orbitopathy?
- 271 What Can I Conclude and Should I Apply the GO-QoL in My Own Practice?
- 272 References

# 275 Socioeconomic Impact

Kahaly, G.J. (Mainz)

- 275 Is There an Actual Cost Estimation of Thyroid Disorders in Germany and/or Europe?
- 276 Does Graves' Orbitopathy Lead to Occupational Disability?
- 276 How Were Data Obtained on Occupational Disability and Impaired Earning Capacity in Graves' Orbitopathy?
- 277 What Are the Findings of the Performed Prospective Study?
- 279 How Should We Interpret the Data Obtained on Occupational Disability and Impaired Earning Capacity in Patients with Graves' Orbitopathy?
- 279 What Are the Relevant Implications for the Daily Clinical Practice?
- 280 Do We Have Data on the Public Health Relevance of Graves' Orbitopathy?
- 283 References

#### 285 The Patient's View

von Arx, G. (Olten); Ayvaz, G. (Ankara)

- 285 Due to the Changes of My Eyes and Skin I Have Not Only "Lost My Face"! Where Can I Get Support and Help?
- 286 Will the Treatment for the Thyroid Make the Eyes Better or Worse?
- 286 Can Graves' Orbitopathy Be Prevented?
- 287 Will My Eyes Always Get Worse?
- 287 What Can Be Done about Common Eye Symptoms of Graves' Orbitopathy?
- 288 Will the Eyes Go Back to Normal?
- 288 The Changes in My Face Have Affected Me Badly. Can Anything Be Done about Them? Shall I Have My Face Back at the End of Treatment?
- 288 Are There Any Risk Factors for a Progressive and Severe Graves' Orbitopathy?
- 289 Can I Contact Patient Support Groups or Fellow Patients?
- 289 If Graves' Orbitopathy Is an Autoimmune Disease, Does That Mean My Immune System Is Collapsed?
- 290 After Orbital Radiation, When Will It Be Possible to Have a Baby?

# 291 Atypical Manifestations

Daumerie, C. (Brussels); Fichter, N. (Olten)

- 291 What Are the Atypical Manifestations of Graves' Orbitopathy?
- 291 What Are Other Diseases Mimicking Unilateral or Atypical Graves' Orbitopathy?
- 292 Are the Clinical Presentation and Management of Unilateral Different from Bilateral Graves' Orbitopathy?
- 295 What Is the Prevalence of Unilateral Graves' Orbitopathy?
- 296 Can We Predict the Course of Unilateral Graves' Orbitopathy?
- 297 What Is Euthyroid/Hypothyroid Graves' Orbitopathy?
- 297 How Will You Manage Euthyroid/Hypothyroid Graves' Orbitopathy?
- 298 What Is Globe Subluxation?
- 298 Can Graves' Orbitopathy Patients without Muscle Swelling Be at Risk for Loss of Vision due to Optic Neuropathy?
- 299 References

# 301 Childhood Graves' Orbitopathy

Bartalena, L. (Varese)

- 301 How Frequent Is Graves' Orbitopathy in Children?
- 302 Are Signs and Symptoms of Graves' Orbitopathy in Childhood Similar to Those in Adulthood?
- 304 Why Is Graves' Orbitopathy in Children and Adolescents Milder than in Adults?
- 305 What Medical Treatment for Graves' Orbitopathy in Children and Adolescents?
- 305 What Modality of Treatment for Hyperthyroidism in Children/Adolescents with Graves' Orbitopathy?
- 306 What about Orbital Decompression in Childhood?
- 306 References

#### 309 Comorbidity in Graves' Orbitopathy

Žarković, M., Knežević, M. (Belgrade)

- 309 What Is the Risk of Diabetes Mellitus in Graves' Orbitopathy?
- 311 What Is the Risk of Osteoporosis in Graves' Orbitopathy?
- 312 What Is the Risk of Mental Disorders in Graves' Orbitopathy?
- 313 What Is the Risk of Dry Eye Syndrome in Graves' Orbitopathy?
- 316 What Is the Risk of Glaucoma in Graves' Orbitopathy?
- 317 What Is the Risk of Cataract in Graves' Orbitopathy?
- 318 What Is the Risk of Retinopathy in Graves' Orbitopathy?
- 318 References

## 322 Prevention

Marcocci, C.; Marinò, M. (Pisa)

- 322 What Is Primary, Secondary, and Tertiary Prevention?
- 322 What Variables Can Be Modified in the Prevention of Graves' Orbitopathy?
- 323 What Can Be Done in Primary and Secondary Prevention of Graves' Orbitopathy?
- 325 What Can Be Done in Tertiary Prevention of Graves' Orbitopathy?
- 327 What Should One Do when Talking to a Graves' Orbitopathy Patient Who Smokes?
- 327 References

# 330 Protocols of Non-Surgical Therapies

Bartalena, L. (Varese)

- 330 What Is the Protocol for Selenium?
- 330 What Is the Protocol for Intravenous Glucocorticoids?
- 332 What Is the Protocol for Oral Glucocorticoids?
- 333 What Is the Protocol for Orbital Radiotherapy?
- 334 What Is the Protocol for Cyclosporine?
- 335 What Is the Protocol for Rituximab?
- 336 References

# 338 The Amsterdam Declaration on Graves' Orbitopathy

Perros, P. (Newcastle upon Tyne)

- 338 What Is the Amsterdam Declaration?
- 339 Why Was It Proposed?
- 340 Have the Targets Been Met?
- 340 Appendix 1: The Amsterdam Declaration
- 341 Appendix 2: Signatories of the Amsterdam Declaration
- 343 References

#### 345 Historical Notes on Graves' Disease

Perros, P. (Newcastle upon Tyne)

- 345 Why Bother about History?
- 346 What Is the Earliest Recorded Case of Graves' Disease and Graves' Orbitopathy?
- 347 What Were the Early Theories about Graves' Disease and Graves' Orbitopathy?
- 348 Who Were the Most Important Contributors in Developing Our Understanding and Treatment of Graves' Orbitopathy?
- 348 What Lessons Should Be Learnt from the History of Graves' Disease and Graves' Orbitopathy?
- 349 References
- 351 Author Index
- 352 Subject Index