

Contents

Introduction	17
1.1. History and Terminology	17
1.2. Pompe Disease as Lysosomal Glycogen Storage Disorder	19
1.3. Epidemiology	20
From Genetic Defect to Clinical Symptoms	23
2.1. In General	23
2.2. From the GAA Gene to Functional Lysosomal GAA	24
2.2.1. GAA pre-mRNA Splicing	24
2.2.2. Translation, Post-Translational Processing and Intracellular Transport	25
2.3. From GAA Deficiency to Cellular Pathology	27
2.3.1. GAA Deficiency and Ensuing Cellular Damage	27
2.3.2. Rescue of Damaged Muscle Tissue by Satellite Cells	29
2.4. The Genotype-Phenotype Correlation	29
2.5. The Pompe Variant Database and the Pompe Registry	32
2.6. Summary	33
Autophagy and its Role in the Pathogenesis of Pompe Disease	38
3.1. Autophagy: Background	38
3.2. Autophagy in Pompe Disease: Focus on Skeletal Muscle	40
3.3. Conclusion	43
Clinical Spectrum	46
4.1. Classic Infantile Pompe Disease	46
4.1.1. Clinical Presentation, Diagnosis, and Natural Course of Disease	46
4.1.2. The New Phenotype	50
4.2. Childhood Pompe Disease	53
4.3. Adult Pompe Disease	55
4.3.1. Clinical Findings	55
Diagnosis	65
5.1. Clinical Chemistry	65
5.2. Muscle Imaging Procedures	66
5.2.1. Infants and Children with Pompe Disease	66
5.2.2. Adult Pompe Disease	67
5.3. Examination of the Cerebral Vessels	69
5.4. Examination of Cardiac Function	70
5.5. Examination of Pulmonary Function	71
5.6. Electromyographic Examination	71
5.7. Muscle Biopsy	71
5.8. Measurement of Enzyme Activity	74
5.9. DNA Analysis	75

6.	Prenatal Diagnosis, Population Screening and Counselling	82
6.1.	Introduction	82
6.2.	Prenatal Diagnosis	82
6.3.	Preimplantation Genetic Testing (PGT)	83
6.4.	Newborn and Population Screening	84
7.	Differential Diagnosis of Pompe Disease	88
7.1.	Differential Diagnosis of Classic Infantile Pompe Disease	88
7.2.	Differential Diagnosis of Childhood Pompe Disease	90
7.3.	Differential Diagnosis of Pompe Disease in Adults	92
7.3.1.	HyperCKemia	92
7.3.2.	Fatigue and Myalgia	92
7.3.3.	Proximal and Axial Muscle Weakness	93
7.3.4.	Rigid Spine Syndrome	94
7.3.5.	Respiratory Impairment	94
8.	Respiratory Impairment in Pompe Disease	97
8.1.	Weakness of the Respiratory Muscle System in Pompe Disease	97
8.1.1.	Respiratory Impairment in Classic Infantile Pompe Disease	97
8.1.2.	Respiratory Impairment in Adult Pompe Disease	97
8.1.3.	Consequences of Respiratory Muscle Weakness	98
8.1.4.	The Course of Respiratory Muscle Weakness	99
8.2.	Respiratory Function Testing	99
8.2.1.	Pulmonary Function Tests (PFTs)	99
8.2.2.	Respiratory Muscle Function and Manometry	99
8.2.3.	Polysomnography	100
8.3.	Management of Respiratory Insufficiency	101
8.3.1.	Respiratory Muscle Training (RMT)	101
8.3.2.	Mechanical Ventilation	101
8.3.3.	Cough Augmentation Techniques	102
8.3.4.	Respiratory Function under Enzyme Replacement Therapy	102
9.	Enzyme Replacement Therapy in Pompe Disease	105
9.1.	The History and Development of ERT with a Focus on Pompe Disease	105
9.2.	Basic Principles of ERT	108
9.3.	Enzyme Replacement Therapy in Infants	111
9.3.1.	The First Trials	111
9.3.2.	ERT for Infants and Children in Clinical Practice: Achievements and Unmet Medical Needs	114
9.3.3.	Dosing	116
9.3.4.	CRIM Status	117
9.3.5.	Antibody Formation	117
9.4.	Immunomodulation under Enzyme Replacement Therapy	118
9.5.	Enzyme Replacement Therapy in Children	122
9.6.	Enzyme Replacement Therapy in Adults	124
9.6.1.	Alglucosidase Alfa Studies in Adults: Late Onset Treatment Study (LOTS)	124
9.6.2.	Alglucosidase Alfa Studies in Adults: Real World Data	125
9.6.3.	Alglucosidase Alfa Studies in Adults: 10-year Data and Unmet Needs	126
9.6.4.	Second Generation ERT	126
9.7.	Gene Therapy	128

	Exercise Training and Rehabilitation Management in Pompe Disease	141
10.1.	Exercise Training	141
10.1.1.	Exercise.....	141
10.1.2.	Effect of Endurance and Resistance Exercise in Pompe Disease	142
10.1.3.	Exercise in Treatment Naive Patients.....	142
10.1.4.	Adverse Effects of Exercise	142
10.2.	Rehabilitation Management of Adults	143
10.2.1.	Presymptomatic Patients	143
10.2.2.	Ambulant and Less Affected Patients	144
10.2.3.	Severely Affected and Wheelchair-Bound Patients	144
10.2.4.	The New Phenotypes.....	144
10.3.	Rehabilitation Management of Patients with Classic Infantile Pompe Disease	145
	Dietary Aspects of Pompe Disease	149
11.1.	Body Mass Index and Body Composition	149
11.2.	Protein Degradation and Energy Expenditure.....	150
11.3.	Optimal Composition of Diet in Pompe Disease.....	151
11.4.	Separate Supplementation of Different Amino Acids.....	151
11.5.	Dietary Suggestions for Pompe Patients in Clinical Practice	152
	Patient Support Groups	155
	Abbreviations	158
	Index	159