Atherosclerosis 235 (2014) 21–30

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

Lysosomal acid lipase deficiency – An under-recognized cause of dyslipidaemia and liver dysfunction

Željko Reiner [a,*], Ornella Guardamagna [b], Devaki Nair [c], Handrean Soran [d], Kees Hovingh [e], Stefano Bertolini [f], Simon Jones [g], Marijana Ćorić [a], Sebastiano Calandra [h], John Hamilton [i], Terence Eagleton [j], Emilio Ros [k,l,**]

[a] University Hospital Center, School of Medicine, University of Zagreb, Kispaticeva 12, 10000 Zagreb, Croatia
[b] Department of Public and Health Sciences, Medical School, University of Turin, Piazza Polonia 94, I-10126 Turin, Italy
[c] Department of Clinical Biochemistry, Royal Free Hospital NHS Foundation Trust, Pond Street, London NW3 2QG, UK
[d] Cardiovascular Trials Unit, Central Manchester University Hospitals NHS Foundation Trust, Oxford Road, Manchester M13 9WL, UK
[e] Department of Vascular Medicine, Academic Medical Center, Meibergdreef 9, Amsterdam 1105 AZ, Netherlands
[f] Department of Internal Medicine, University of Genoa, Viale Benedetto XV n. 6, 16132 Genoa, Italy
[g] Willink Biochemical Genetics Unit, Manchester Centre for Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust, St. Mary's Hospital, Oxford Road, Manchester M13 9WL, UK
[h] Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Via Campi 287, I-41125 Modena, Italy
[i] Biochemistry Department, Yorkhill Hospital, Glasgow, G3 8SJ, UK
[j] Synageva BioPharma Corp., 33 Hayden Ave., Lexington, MA 02421, USA
[k] Lipid Clinic, Endocrinology & Nutrition Service, Institut d'Investigations Biomèdiques August Pi Sunyer, Hospital Clínic, C. Villarroel, 170, 08036 Barcelona, Spain
[l] CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn), Instituto de Salud Carloss III (ISCIII), Spain

ARTICLE INFO

Article history:
Received 20 December 2013
Received in revised form
4 April 2014
Accepted 5 April 2014
Available online 15 April 2014

Keywords:
Cholesteryl ester storage disease
Dyslipidaemia
Hepatomegaly
Lysosomal acid lipase deficiency
Wolman disease

ABSTRACT

Lysosomal acid lipase deficiency (LAL-D) is a rare autosomal recessive lysosomal storage disease caused by deleterious mutations in the *LIPA* gene. The age at onset and rate of progression vary greatly and this may relate to the nature of the underlying mutations. Patients presenting in infancy have the most rapidly progressive disease, developing signs and symptoms in the first weeks of life and rarely surviving beyond 6 months of age. Children and adults typically present with some combination of dyslipidaemia, hepatomegaly, elevated transaminases, and microvesicular hepatosteatosis on biopsy. Liver damage with progression to fibrosis, cirrhosis and liver failure occurs in a large proportion of patients. Elevated low-density lipoprotein cholesterol levels and decreased high-density lipoprotein cholesterol levels are common features, and cardiovascular disease may manifest as early as childhood. Given that these clinical manifestations are shared with other cardiovascular, liver and metabolic diseases, it is not surprising that LAL-D is under-recognized in clinical practice. This article provides practical guidance to lipidologists, endocrinologists, cardiologists and hepatologists on how to recognize individuals with this life-limiting disease. A diagnostic algorithm is proposed with a view to achieving definitive diagnosis using a recently developed blood test for lysosomal acid lipase. Finally, current management options are reviewed in light of the ongoing development of enzyme replacement therapy with sebelipase alfa (Synageva BioPharma Corp., Lexington, MA, USA), a recombinant human lysosomal acid lipase enzyme.

* Corresponding author. Tel.: +385 1 2376041; fax: +385 1 2388623.
** Corresponding author. Lipid Clinic, Endocrinology & Nutrition Service, Institut d'Investigations Biomèdiques August Pi Sunyer, Hospital Clínic, C. Villarroel, 170, 08036 Barcelona, Spain. Tel.: +34 93 2279383; fax: +34 934537829.
E-mail addresses: zreiner@kbc-zagreb.hr (Ž. Reiner), eros@clinic.ub.es (E. Ros).

http://dx.doi.org/10.1016/j.atherosclerosis.2014.04.003

Contents

1. Introduction 22
2. Current understanding of lysosomal acid lipase deficiency 22
2.1. Inheritance and genetics 23
2.2. Pathogenesis 23
3. Signs and symptoms of lysosomal acid lipase deficiency 24
3.1. Dyslipidaemia 25
3.2. Effects on the liver and spleen 25
4. Differential diagnoses 25
5. Screening for lysosomal acid lipase deficiency 25
6. Investigations to diagnose LAL-D 26
6.1. Measurement of LAL activity 26
6.2. Genetic testing 27
6.3. Liver biopsy 27
6.4. Radiological techniques 27
7. Management and therapies in development 27
7.1. Lipid-lowering therapies 27
7.2. Vitamin E 27
7.3. Haematopoietic stem cell and liver transplantation 28
7.4. Enzyme replacement therapy 28
8. Disease monitoring 28
9. Prognosis 28
10. Discussion 28
Declaration of conflicts of interest 28
Acknowledgements 29
Supplementary data 29
References 29

1. Introduction

Lysosomal acid lipase deficiency (LAL-D) is a rare autosomal recessive lysosomal storage disease characterized by progressive accumulation of cholesteryl esters and triglycerides in the liver, spleen and other organs [1]. Dyslipidaemia is a common finding in patients with LAL-D that has been associated with accelerated development of atherosclerosis, cardiovascular disease and premature mortality [1–3]. Progressive liver disease is another characteristic feature of LAL-D, and patients typically present with hepatomegaly, elevated transaminase levels and/or microvesicular steatosis [1].

LAL-D is an under-recognized condition, with many affected individuals receiving no diagnosis or incorrect diagnoses of heterozygous familial hypercholesterolaemia (HeFH), familial combined hyperlipidaemia (FCH), non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD) or cryptogenic cirrhosis [4–6]. This review paper aims to provide recommendations to guide the timely diagnosis of LAL-D.

2. Current understanding of lysosomal acid lipase deficiency

LAL-D is a heterogeneous disease that presents along a clinical continuum, with signs and symptoms and rate of progression varying between affected individuals [1]. The most rapidly progressive presentation occurs in infants, was first described in 1956 and is referred to as Wolman disease [7]. A few years later, Fredrickson reported the case of a 12-year-old boy with marked hypercholesterolaemia, hepatomegaly and cholesteryl ester accumulation on liver biopsy [8]. This later-onset condition was named cholesteryl ester storage disease (CESD). Since their initial characterization, it has been discovered that Wolman disease and CESD share the same underlying molecular pathology, resulting from mutations in the *LIPA* gene, which encodes lysosomal acid lipase (LAL), the enzyme responsible for hydrolysing the cholesteryl esters and triglycerides within low density lipoprotein (LDL) particles into free cholesterol and free fatty acids [9–12]. The variable rates of progression observed between patients with LAL-D are believed to be related to the nature of the disease-causing mutations and the resulting degree of residual enzyme activity [10,11]. However, there may be other contributing factors (e.g. environmental influences) affecting disease progression.

Infants with LAL-D typically present in the first weeks of life and die within 6–12 months due to multi-organ failure [10]. Clinical signs may even arise during pregnancy, with reports of foetal ascites and polyhydramnios detected by prenatal ultrasonography [13]. The hallmarks of the disease in infants consist of prominent hepatosplenomegaly, diarrhoea and vomiting, resulting in malabsorption, growth failure and liver failure. These infants quickly develop liver fibrosis and cirrhosis due to the massive accumulation of cholesteryl esters and triglycerides in the liver [14]. Abnormal lipid accumulation has also been described in the spleen, adrenal glands, lymph nodes, intestinal mucosa, vascular endothelium and skeletal muscle [14,15]. Approximately 50% of infants with LAL-D have adrenal calcifications [1,16].

In children and adults, LAL-D has a more variable clinical course than in infants. Mean age at symptom onset has been reported to be 5 years in both male and female patients, although clinical presentation has been documented as late as 44 years old in men and 68 years old in women [1]. Lipid abnormalities may be present at all ages, with a lipid profile that is indistinguishable from that of more common genetic hypercholesterolaemias, such as HeFH [17]. Liver dysfunction is common, with hepatomegaly being an almost universal finding at diagnosis [1,18]. These phenotypic features of LAL-D are non-specific and overlap with other diseases, which may explain the common under-diagnosis of this condition.