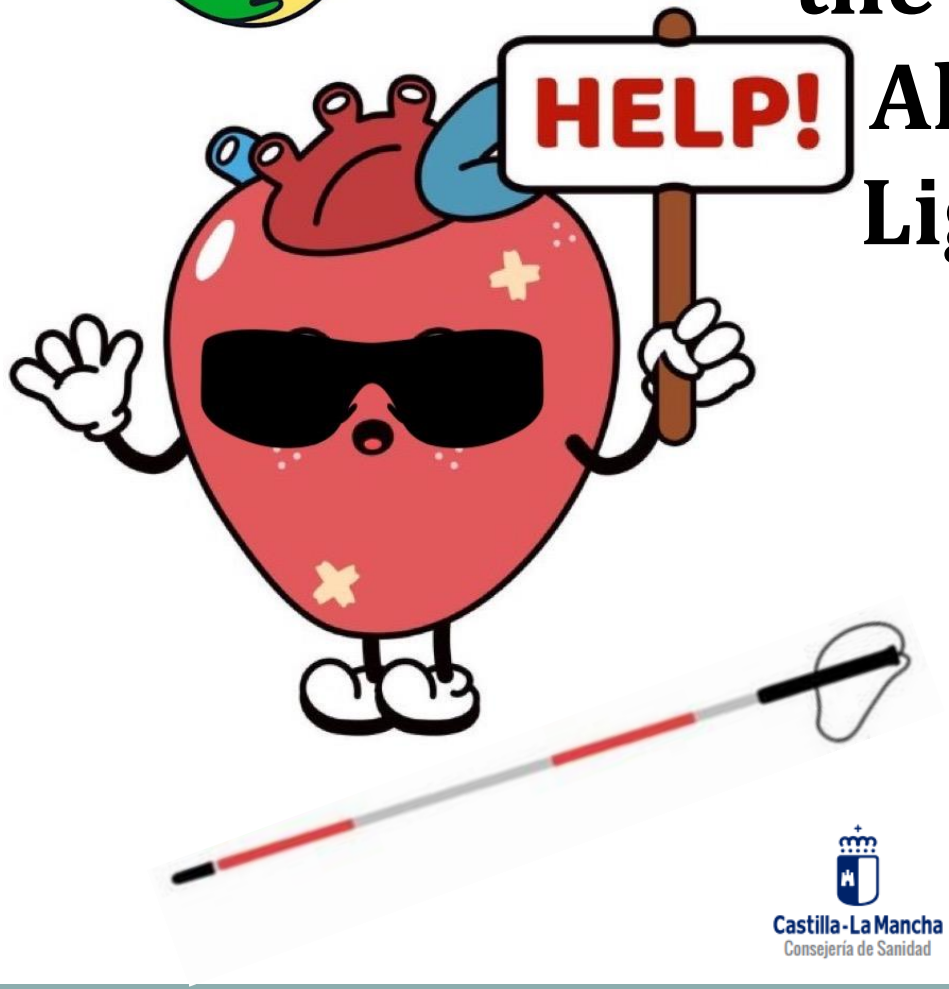
Milestones in the Cardiomyopathy in Alström syndrome: Lights and Shadows



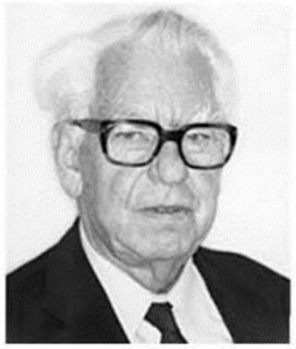
Dr. Alfonso Ortigado
MD, PhD, Pediatrician, Pediatric Cardiologist
Head of the Department of Pediatrics.
Guadalajara Universitary Hospital, Spain.
Professor of Pediatrics.
Faculty of Medicine &Health Sciences
University of Alcala, Madrid, Spain

Baltimore, October 4-9, 2023

Acta Psychiatr Neurol Scand Suppl. 1959;129:1-35.

Retinal degeneration combined with obesity, diabetes mellitus and neurogenous deafness: a specific syndrome (not hitherto described) distinct from the Laurence–Moon–Bardet–Biedl syndrome: a clinical, endocrinological and genetic examination based on a large pedigree

C H ALSTROM, B HALLGREN, L B NILSSON, H ASANDER

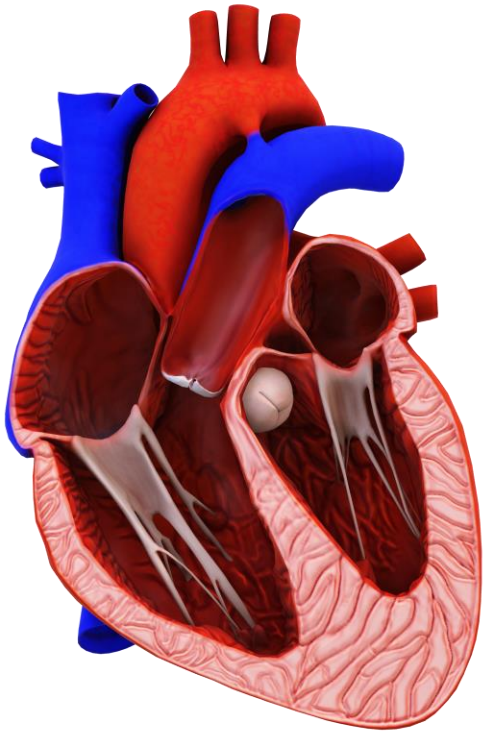


CARL-HENRY ALSTRÖM (1907-1993)

- Carl-Henry Alström was born in Vasteras, Sweden on May 3, 1907.

- He studied Medicine in Stockholm and received his doctorate in psychiatry in **1935** the Karolinska Institute of Medicine.
- At the Serafimerlasarettet Hospital in **1946** that he saw a 14 year old boy who appeared to have symptoms similar to the Laurence-Moon-Bardet-Biedl Syndrome.
- Further investigation revealed that the young man had two second cousins, a boy and a girl about ten years older, with similar but more pronounced features.
-These three patients ere reported in manuscript published in **1959**.

Alström syndrome



“WHAT HAPPENS IN THE HEART?”

Dr. Alfonso Ortigado

THE HEART

1.- **What** is cardiomyopathy?
2.- **Why** does cardiomyopathy appear?
3.- **When** does cardiomyopathy appear?
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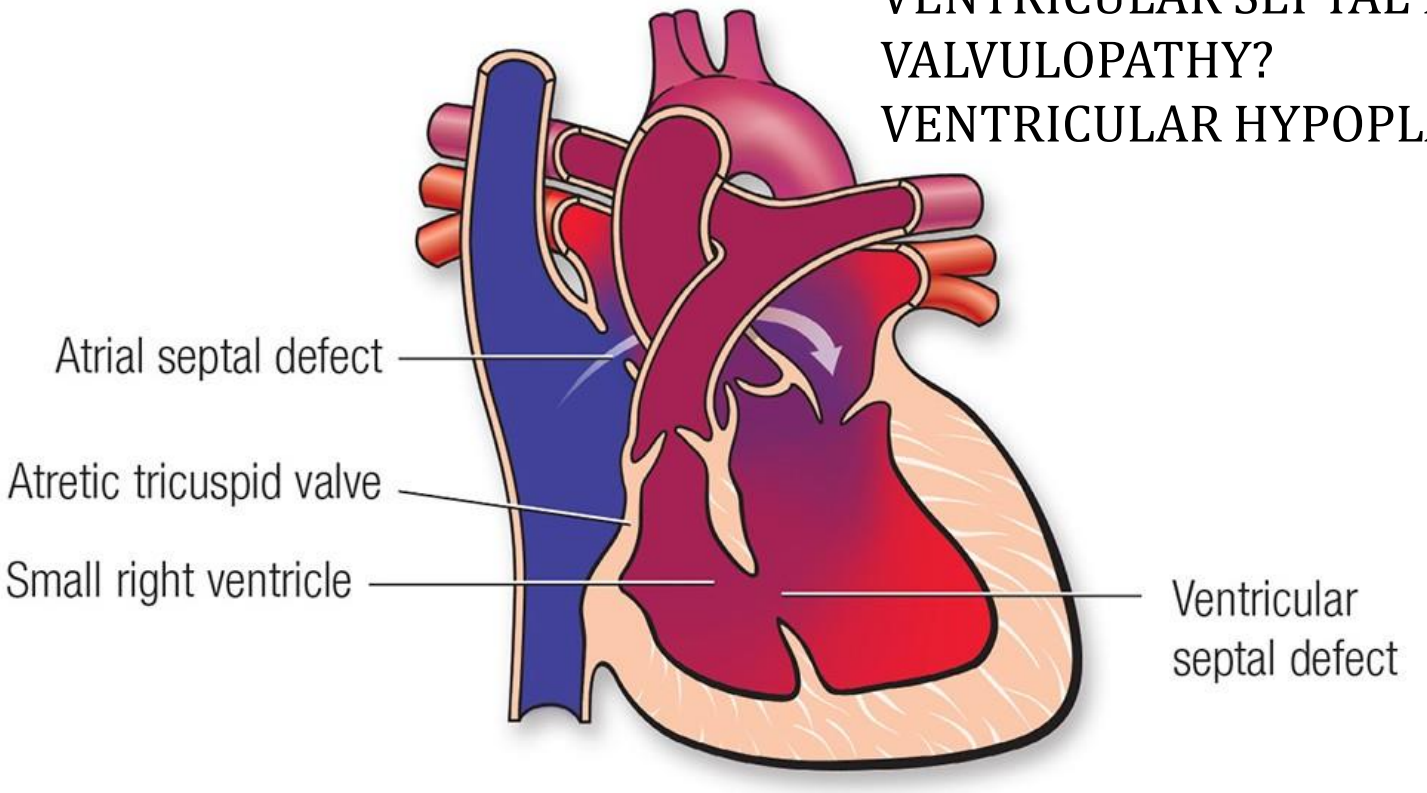
Alström syndrome

"CONGENITAL HEART DISEASE?"

ATRIAL SEPTAL DEFECT?
VENTRICULAR SEPTAL DEFECT?
VALVULOPATHY?
VENTRICULAR HYPOPLASIA?



...öm syndro...

"CO...L HEA...CE?"

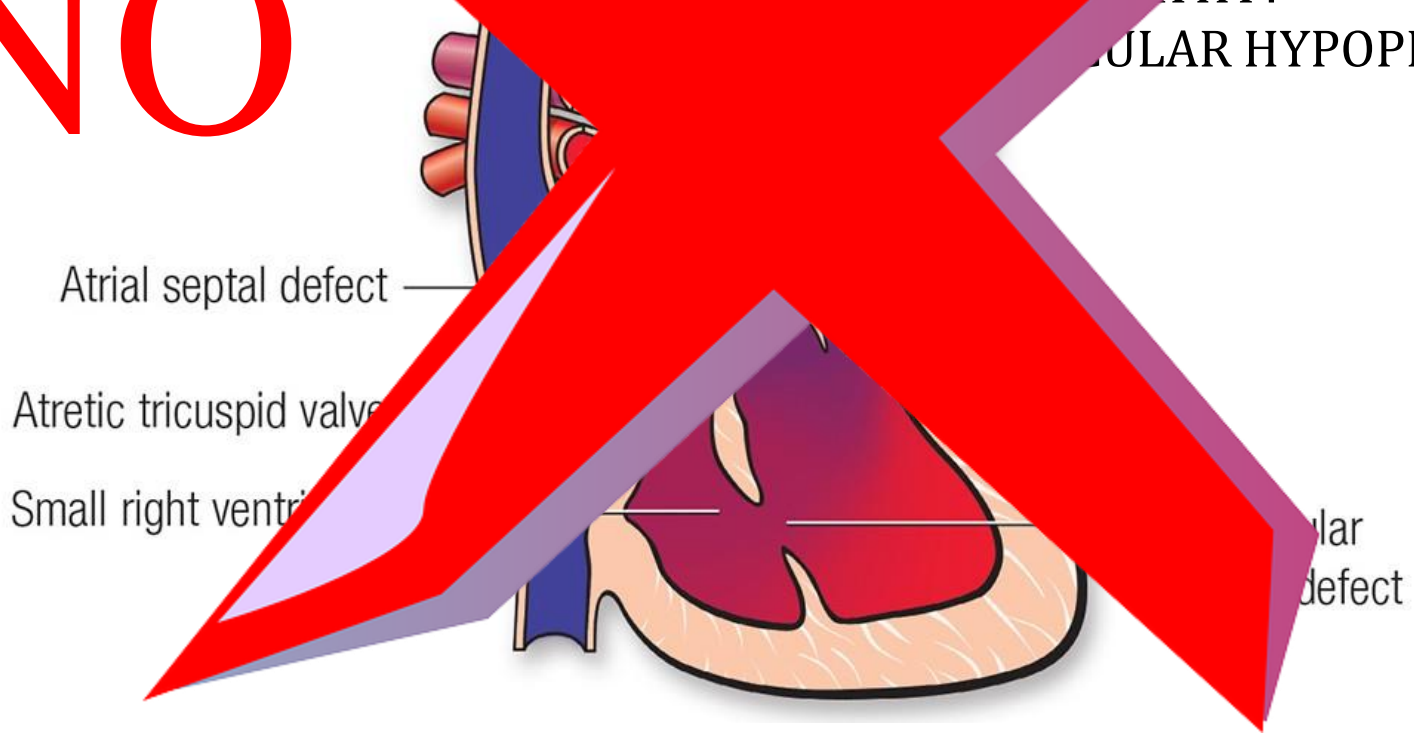
...EFECT?

...SEPTAL DEFECT?

...HY?

...ULAR HYPOPLASIA?

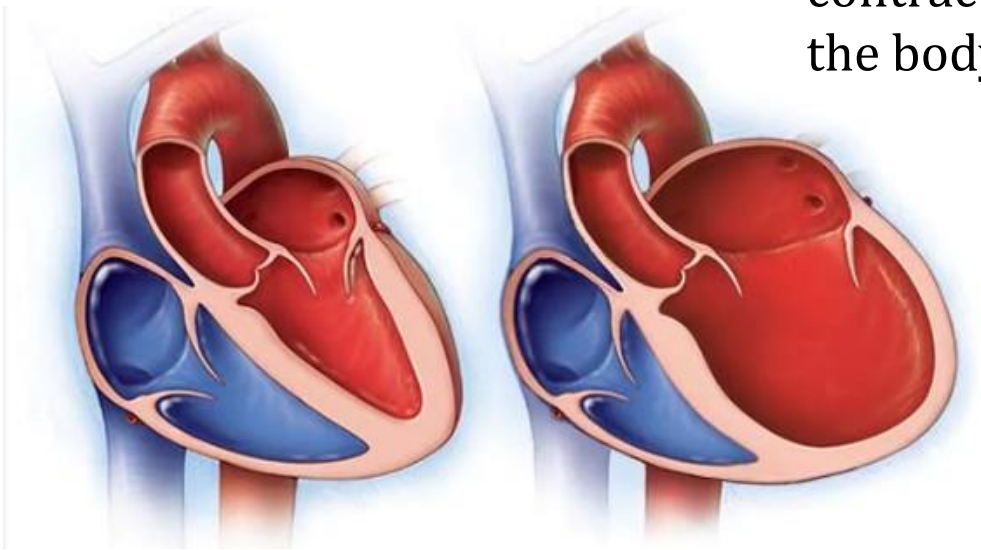
NO



Alström syndrome

"DILATED CARDIOMYOPATHY"

The muscle walls of the heart become stretched and thin, so they cannot contract properly to pump blood around the body.



This desease is characterized by dilatation and impaired function of the left or both ventricules.

HEART MUSCLE DIDEASE

"MYOCARDIAL FIBROSIS"
Diffuse intersticial fibrosis

NORMAL DILATED CARDIOMYOPATHY

THE HEART

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Arch Intern Med. 2005 Mar 28;165(6):675-83. doi: 10.1001/archinte.165.6.675.

New Alström syndrome phenotypes based on the evaluation of 182 cases

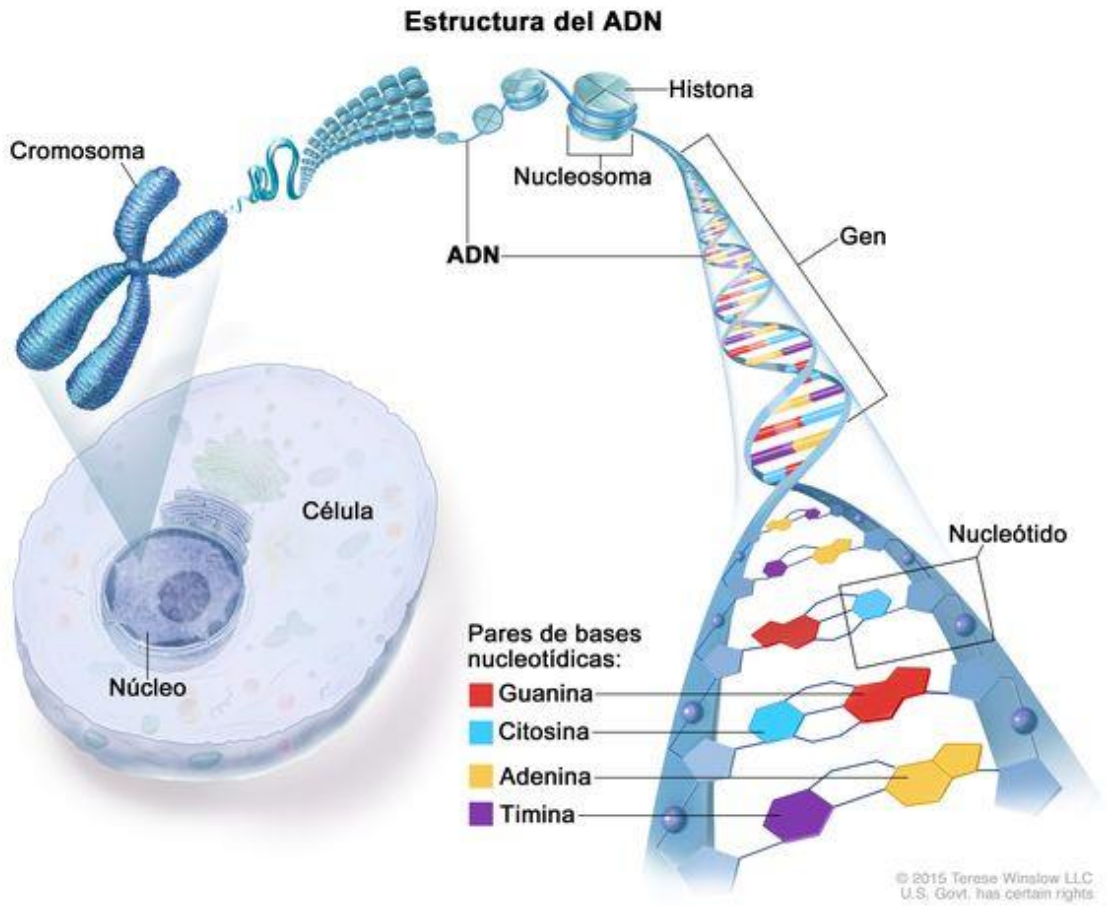
Jan D Marshall [1], Roderick T Bronson, Gayle B Collin, Anne D Nordstrom, Pietro Maffei, Richard B Paisey, Catherine Carey, Seamus Macdermott, Isabelle Russell-Eggitt, Sarah E Shea, Judy Davis, Sebastian Beck, Gocha Shatirishvili, Cristina Maria Mihai, Maria Hoeltzenbein, Giovanni Battista Pozzan, Ian Hopkinson, Nicola Sicolo, Jürgen K Naggert, Patsy M Nishina

JAN DAVIS MARSHALL (1948-2016)

The Jackson Laboratory

Alström syndrome

... IS A GENETIC DISEASE



CHROMOSOME

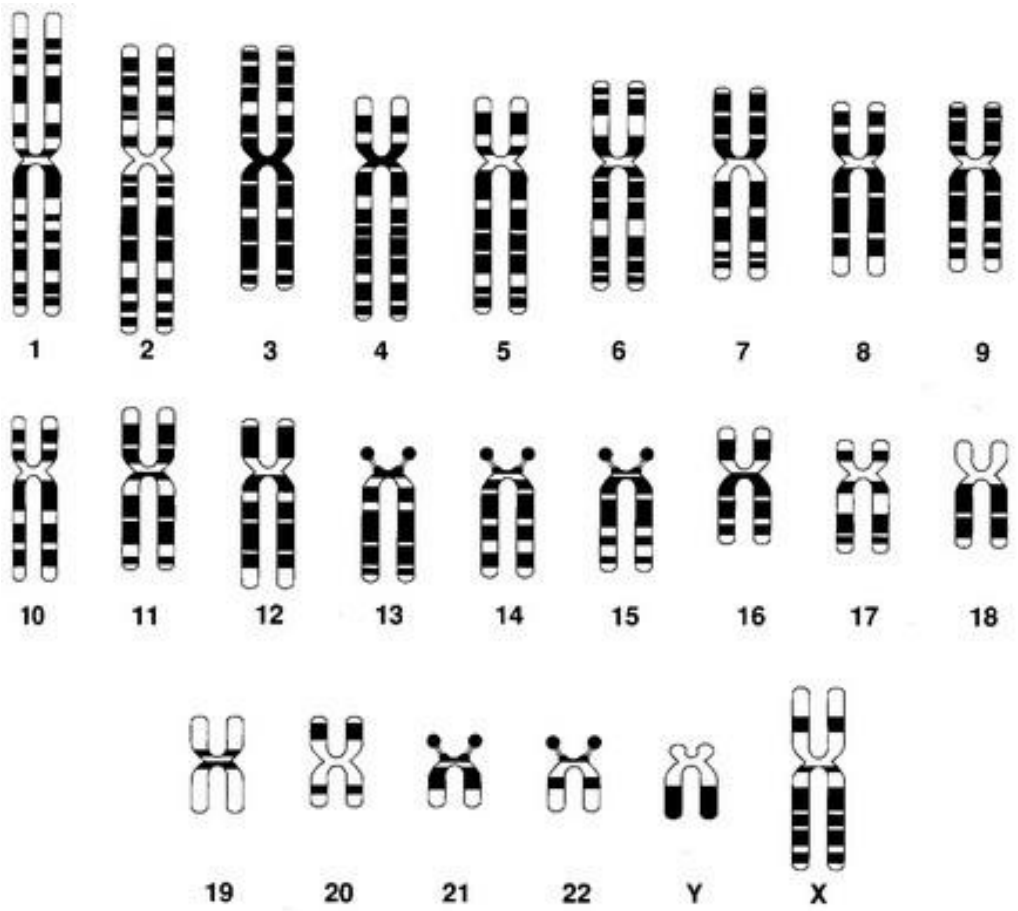
GENE
"CODING SEQUENCE"

PROTEINS

KARIOTYPE

OUR COMPLET SET OF CHROMOSOMES

The typical human karyotype contains 23 pairs of chromosomes



22 pairs of **autosomal chromosomes**

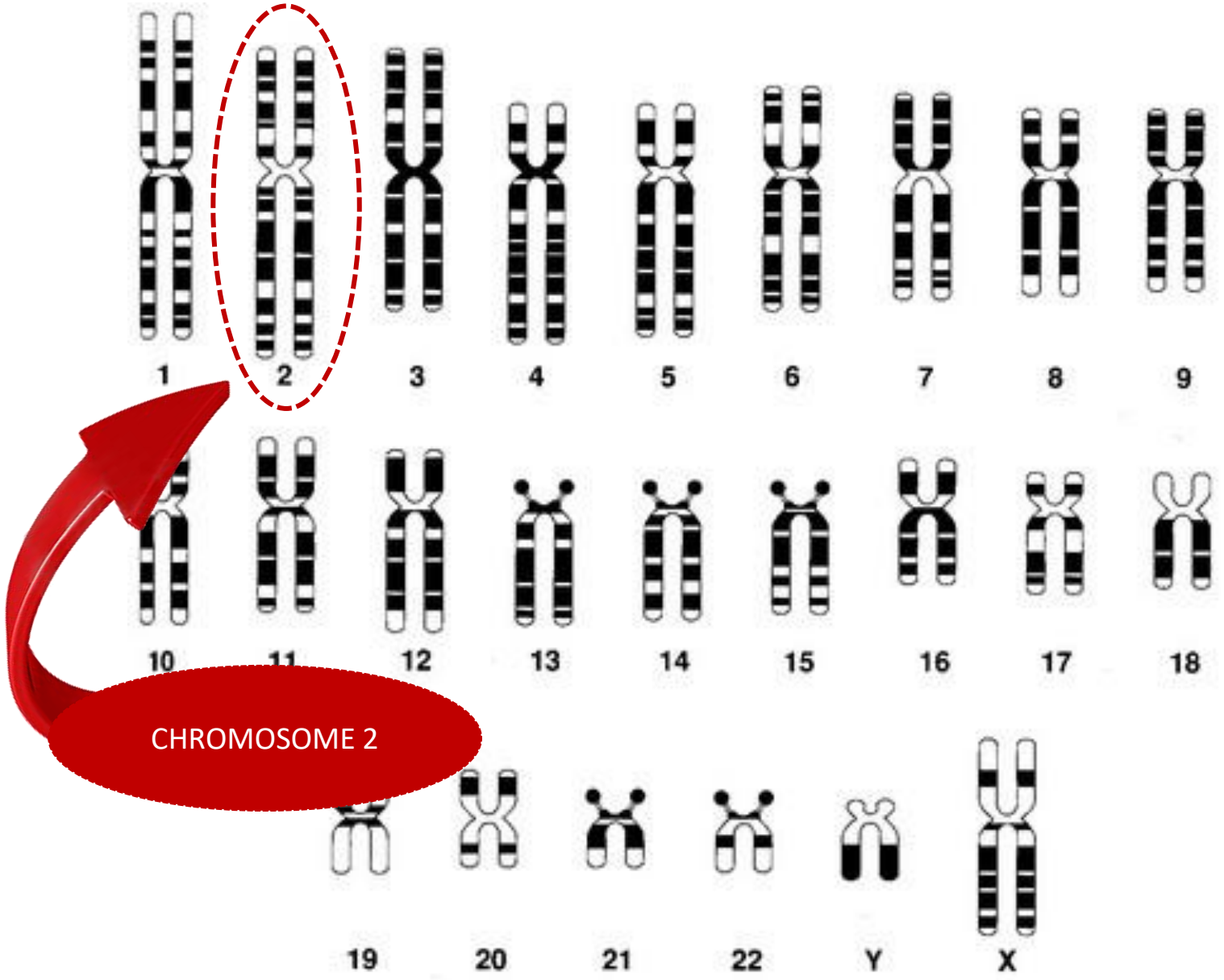
+

1 pair of **sex chromosomes**

Female: XX

Male: XY

23 pairs of chromosomes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CHROMOSOME 2

ALMS1 GENE

Journal of Molecular Medicine (2019) 97:1–17
https://doi.org/10.1007/s00109-018-1714-x

JMolMed

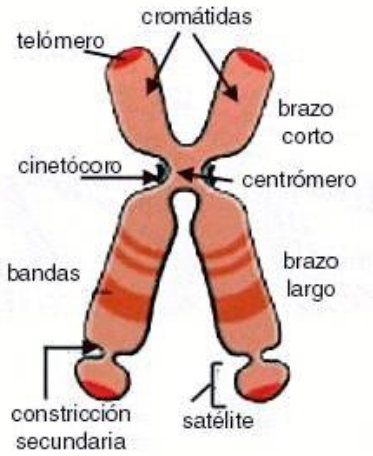
REVIEW

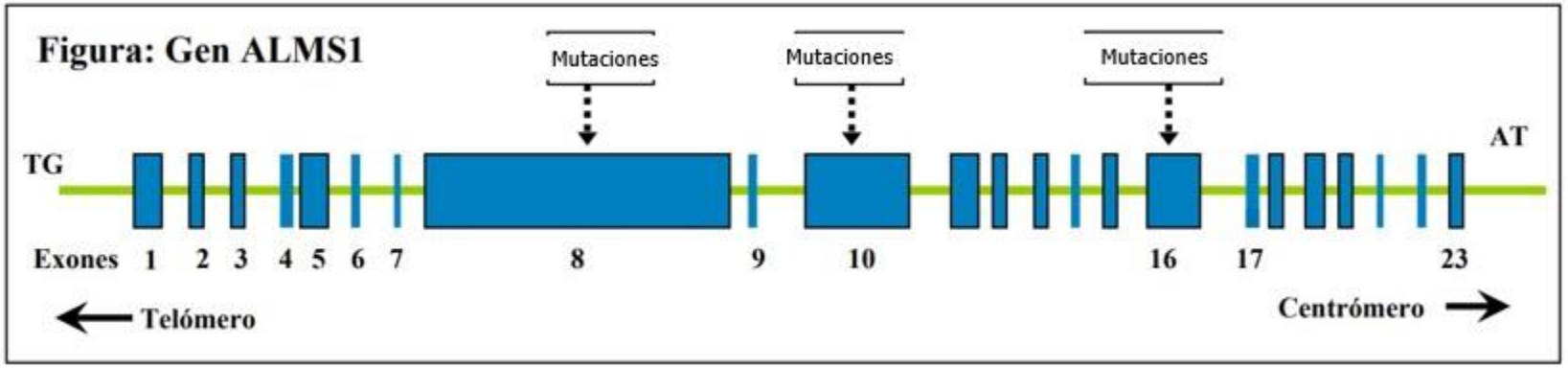
ALMS1 and Alström syndrome: a recessive form of metabolic, neurosensory and cardiac deficits

Tom Hearn[1]

Alström syndrome: OMIM #203800

OMIM: Online Mendelian Inheritance in Man

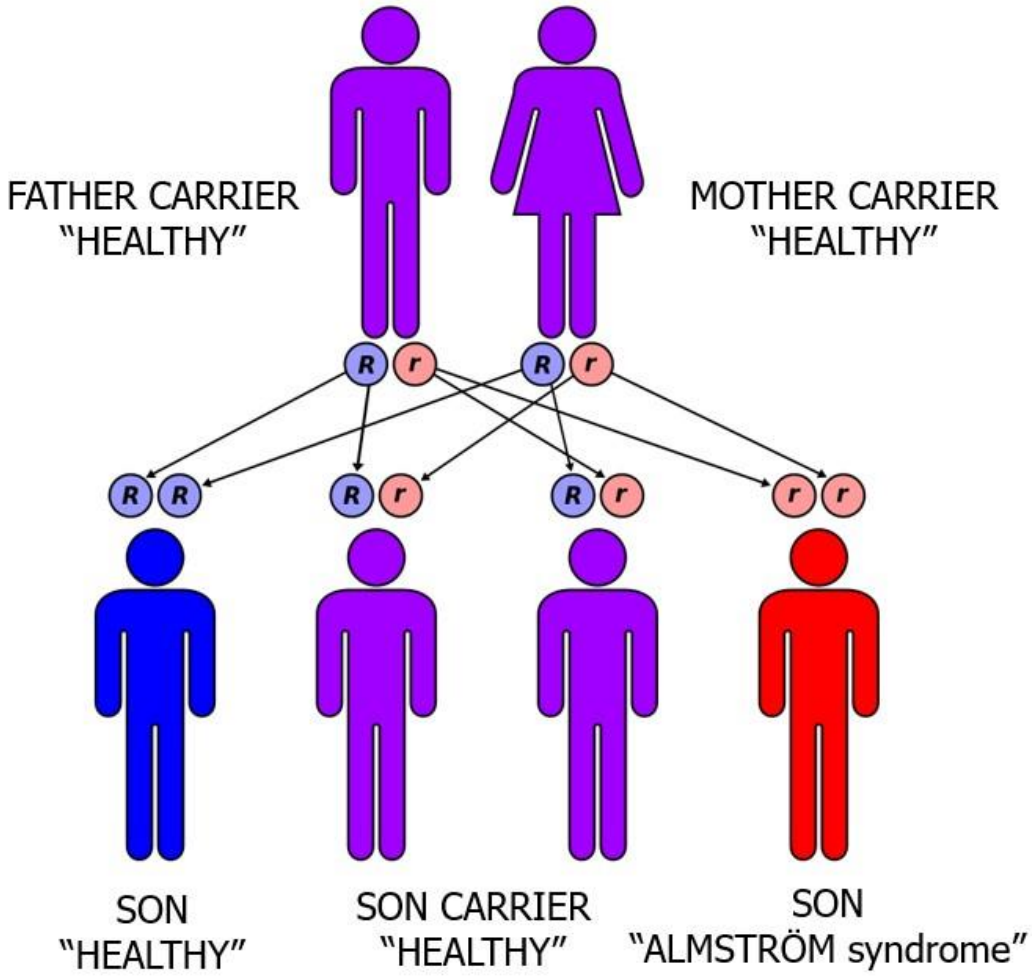




- ALMS1 gene is located on the short arm of **Chromosome 2** (2p13-p12)
- ALMS1 gene encodes the **ALMS1 protein** (4.169 amino acids).
- ALMS1 gene is **complex** with de 23 exones (coding regions)
- **Many mutatios** have been identified (> 200): exon 8, 10 and 16.
- **Autosomal recessive inheritance**: mutation is in both healty parents.
- ALMS1 protein is a **ciliary protein**: centrosomes and basal bodies of ciliated cells
- ALMS1 protein is expressed in **many tissues**: eye, ear, kidney, liver, brain, **heart**…

… IS A GENETIC DISEASE

…is a monogenic autosomal recessive disorder.
…is caused by biallelic variants in ALMS1 gene



The following manifestations are observed in most Alström Syndrome cases:

- Nystagmus and photodysphoria in early infancy
- Progressive pigmentary retinopathy (cone-rod dystrophy) leading to blindness
- Childhood obesity, beginning in the first year and often moderating to high-normal weight in adulthood
- Mild to moderate bilateral sensorineural hearing loss
- Congestive heart failure secondary to dilated cardiomyopathy in infancy or early adulthood
- Normal extremities / absence of polydactyly or syndactyly
- Hyperinsulinemia / insulin resistance
- Type 2 diabetes (or NIDDM) developing in early adulthood
- Elevation of hepatic enzymes and steatosis
- Progressive chronic nephropathy that presents as tubular dysfunction and glomerulosclerosis
- Normal intelligence with some reports of delayed early developmental milestones

ALSTRÖM SYNDROME INTERNATIONAL

ASI

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Manifestations present in some but not all cases include:

- Hypothyroidism
- Splenomegaly
- Portal hypertension
- Hepatic dysfunction
- Alopecia
- Low levels of growth hormone
- Short stature
- Advanced bone age
- Scoliosis and/or kyphosis
- Delay of early developmental milestones
- Hypertension
- Hirsutism, hyperandrogenism
- Hyperlipidemia
- Acanthosis nigricans
- Hyperuricemia
- Male hypogenitalism
- Irregular menses
- Hyperostosis frontalis interna
- Diabetes insipidus
- Frequent urinary tract infections
- Gastrointestinal reflux
- Asthma or respiratory problems
- Hypersecretory lungs
- COPD

GeneReviews

Alström Syndrome

Richard B Paisey, MD, FRCP,[1] Rick Steeds, MD,[2] Tim Barrett, MD,[3] Denise Williams, MD,[4] Tarekegn Geberhiwot, MD,[5] and Meral Gunay-Aygun, MD[6,7]

Created: February 7, 2003; Updated: June 13, 2019.

› Eur J Hum Genet. 2007 Dec;15(12):1193-202. doi: 10.1038/sj.ejhg.5201933. Epub 2007 Oct 17.

Alström syndrome

Jan D Marshall [1], Sebastian Beck, Pietro Maffei, Jürgen K Naggert

Age Range	Diagnostic Criteria		Minimum Required
	Major	Minor	
Birth - 2 yrs [1]	• 1 *ALMS1* pathogenic variant OR family history of Alström syndrome • Nystagmus / photophobia / impaired vision • Infantile cardiomyopathy	• Obesity • SNHL	2 major criteria OR 1 major + 2 minor criteria
3-14 yrs [1]	• 1 *ALMS1* pathogenic variant OR family history of Alström syndrome • Nystagmus / photophobia / impaired vision (if old enough for testing: cone dystrophy by ERG) • History of infantile cardiomyopathy	• SNHL • Obesity &/OR its complications (e.g., insulin resistance, T2DM, liver steatosis, hypertriglyceridemia) • Restrictive cardiomyopathy • ↓ renal function	2 major criteria OR 1 major + 3 minor criteria
15 yrs - adult	• 1 *ALMS1* pathogenic variant OR family history of Alström syndrome • Vision (history of nystagmus in infancy/childhood, impaired vision, legal blindness, cone & rod dystrophy by ERG)	• SNHL • Restrictive cardiomyopathy &/OR history of infantile cardiomyopathy • Obesity &/OR its complications (e.g., insulin resistance, T2DM, liver steatosis, hypertriglyceridemia) • CKD Stage ≥III	2 major + 2 minor criteria OR 1 major + 4 minor criteria

Adapted from Marshall et al [2007]; reprinted with permission of Nature Publishing Group

CKD = chronic kidney disease; ERG = electroretinogram; SNHL = sensorineural hearing loss; T2DM = type 2 diabetes mellitus

1. Children in these age groups should be reevaluated for the presence of major and minor criteria as they age.

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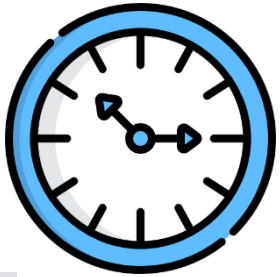
7.- How does cardiomyopathy **develop**?

When does cardiomyopathy appear?

Patients are at risk of sudden abrupt onset of dilated cardiomyoptahy **at any age, but time matters.**



The **early onset** of cardiomyopathy:
Ages between 3 weeks and 4 months (42%)

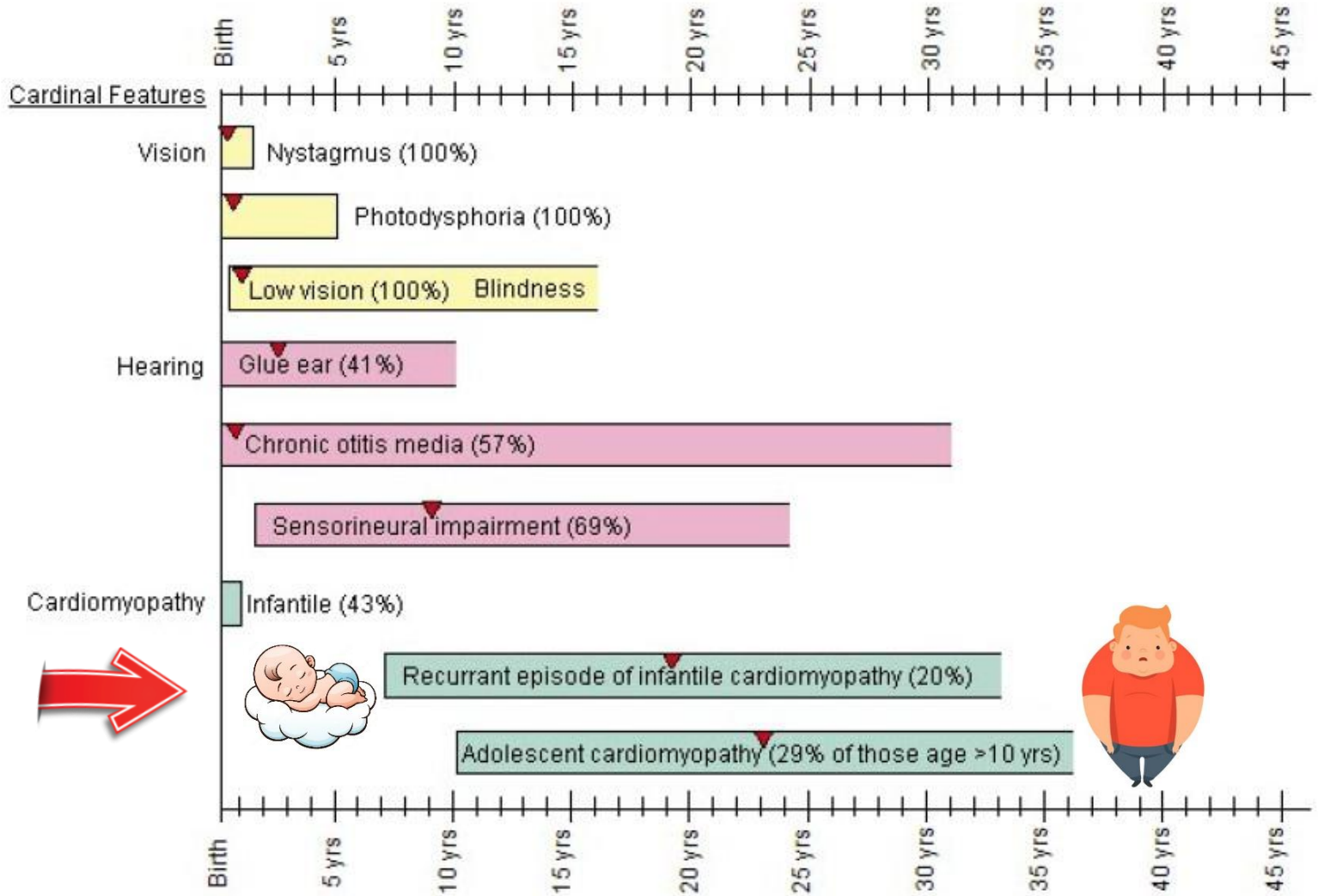
Dilated cardiomyopathy

Cardiomyoptahy can be the **first clinical feature** of the sydrome, prior to the appearance of others

The **later onset** of cardiomyopathy:
Ages between teens and late 30s (18%)

Restrictive cardiomyopathy

When does cardiomyopathy appear?



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How does cardiomyopathy appear?

Younger Children:
- Respiratory distress.
- Abdominal distension.
- Increased sweating.
- Tachycardia
- Poor feeding
- Failure to thrive
- Peripheral edema: uncommon

Older Children:
- Exercise intolerance.
- Dyspnea on exertion
- Tachycardia.
- Palpitations.
- Chest pain.
- Abdominal distention.
- Syncope
- Sudden death.

Cardiomyopathy can be mistaken for a respiratoty infection and confused with it

Cardiomyopathy: diagnostic approach

General study: physician

First, **clinical diagnosis**: if you don't think about it, you won't be able to study it.

- Electrocardiogram: heart rate? Cardiac rhythm? Ventricular hypertrtophy
- Chest radiography: heart size? heart shape? pulmonary circulation?
- Laboratory tests:

1.- Bold count: anemia? Leukocytosis?

2.- Electrolytes:

- Hiponatremia?(expansión of extracelular fluid volumen)
- Hyperkaliemia? (impaired renal perfusion or impaired tissue perfusion)

3.- Renal function?: elevated creatine or BUN (blood urea nitrogen)

4.- Liver function?: elevated liver enzymes (AST, ALT, LDH), hipoalbuminemia

5.- Natriuretic peptides: elevated NT-proBNP, BNP (correlate with Heart Failure)

6.- Cardiac muscle: elevated CPK-MB, Troponin I and T, lactate (myocardial damage)

7.- Arterial blood gas: hipoxemia (impaired tissue perfusion), hipocapnia in early stages progressing to hipercapnia (respiratory acidosis)

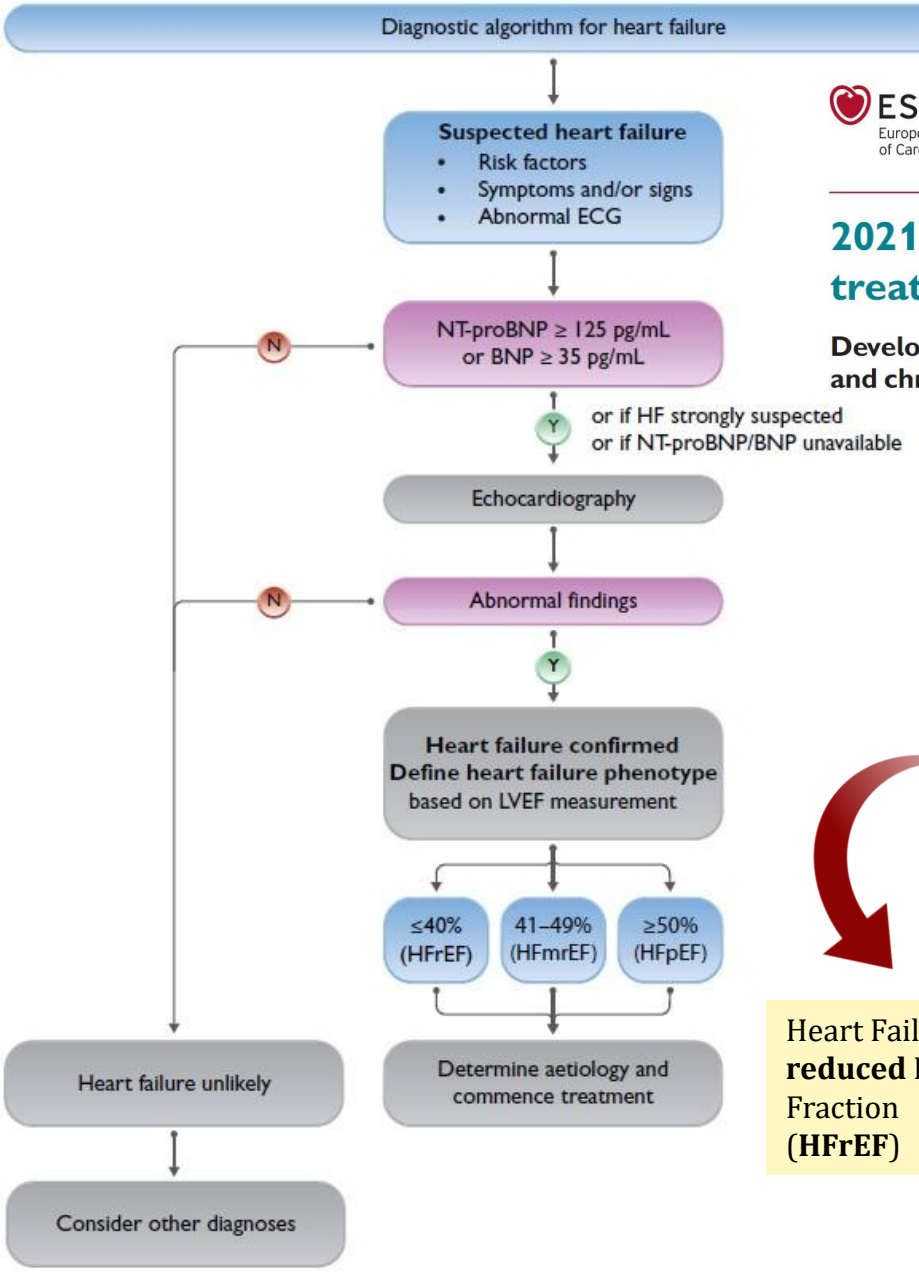
Cardiomyopathy: diagnostic approach

Specific study: cardiologist

- **Echocardiography**:
- Cardiac morphology and structure.
- Chamber volumes/diameters.
- Wall thickness.
- Ventricular systolic/diastolic function
- Pulmonary pressure
- Strain by speckle tracking echocardiography: Global Longitudinal Strain

Advantages of Echocardiography:
1.- Is the most useful
2.- Provides immediate data
3.- Is widely available
4.- Is a low-cost test

- **Cardiac Magnetic Resonance (CMR)**:
- Myocardial Fibrosis: Late Gadolinium enhancement
- Difusse intersticial myocardial fibrosis:
CMR T1 mapping and extracellular volumen quantification

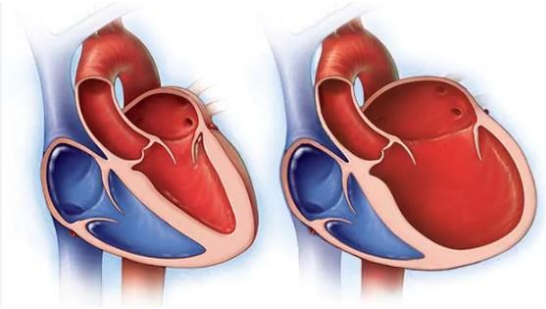


ESC European Society of Cardiology
European Heart Journal (2021) 42, 3599–3726
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)



DILATED CARDIOMYOPATHY

Heart Failure **with reduced** Ejection Fraction **(HFrEF)**

Heart Failure **with mildly reduced** Ejection Fraction **(HFmrEF)**

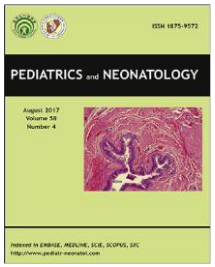
Heart Failure **with preserved** Ejection Fraction **(HFpEF)**

Pediatric Heart failure: pathophysiology

Pediatric Heart Failure: A Practical Guide to Diagnosis and Management

Daniele Masarone*, Fabio Valente, Marta Rubino, Rossella Vastarella, Rita Gravino, Alessandra Rea, Maria Giovanna Russo, Giuseppe Pacileo, Giuseppe Limongelli

Cardiologia SUN – Heart Failure Unit, Department of Cardiothoracic Sciences, Second University of Naples, Naples, Italy



Pediatrics and Neonatology (2017) 58, 303e312

http://dx.doi.org/10.1016/j.pedneo.2017.01.001

Reduced cardiac output

Reduced baroreceptor

Reduced renal perfusion

Compensatory mechanisms:
Activation Sympathetic Nervus System

Increased heart rate
Increased cardiac contractility
Vasoconstriction (increased afterload)

Compensatory mechanisms:
Activation Renin-Angiotensin-Aldosterone System

Vasoconstriction (increased afterload)
Sodium and water retention (increased preload)

Myocardial toxicity

Myocardial apoptosis/Fibrosis

Myocardial dysfunction

Pediatric Heart failure: treatment

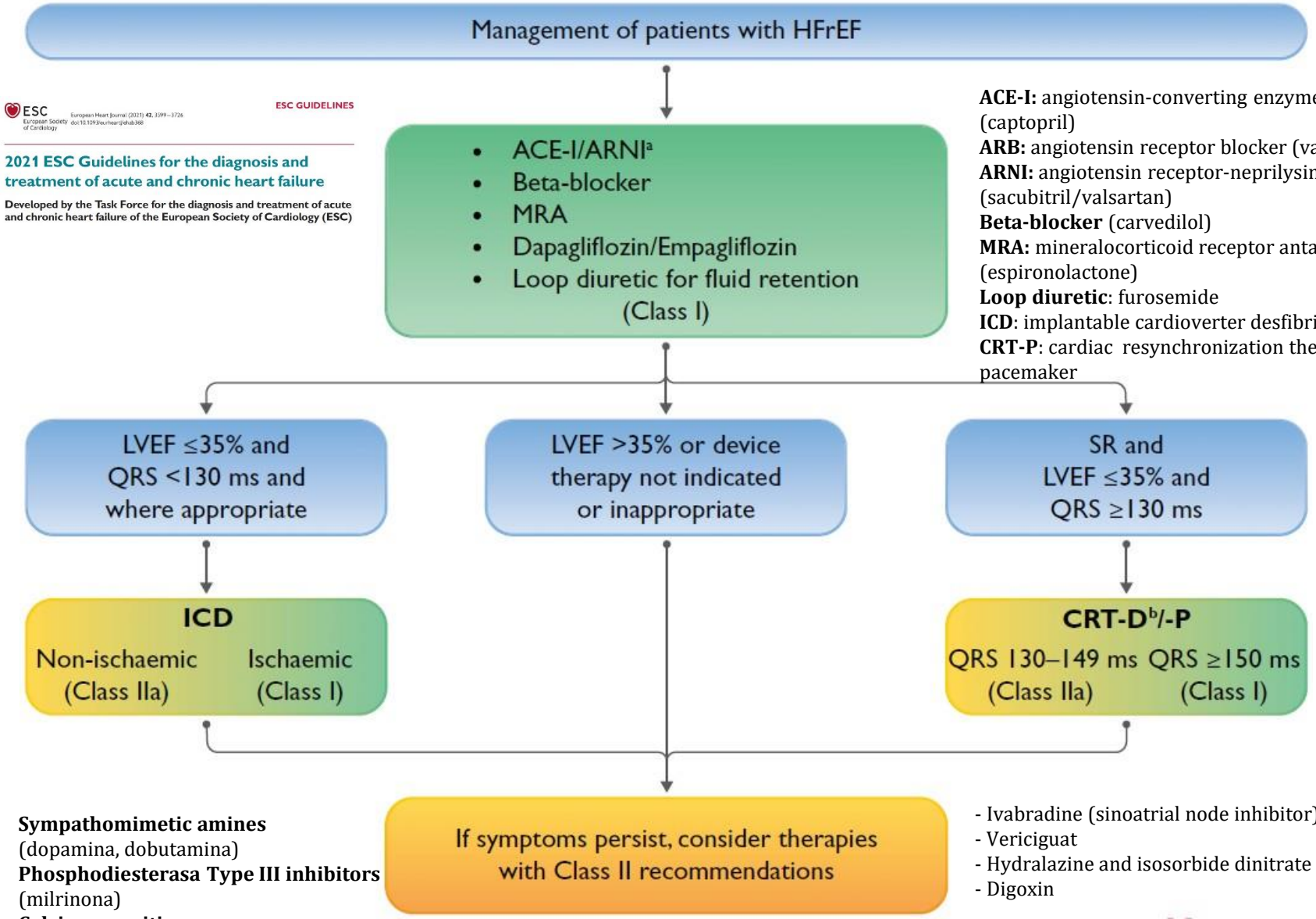
Heart failure

Compensatory mechanisms:
Activation Sympathetic Nervus System

Compensatory mechanisms:
Activation Renin-Angiotensin-Aldosterone System

HARMFUL EFFECTS:
- Increased heart rate
- Sodium and water retention (increased preload)
- Vasoconstriction (increased afterload)
- Ventricular remodeling
- Myocardial apoptosis
- Myocardial fibrosis

- **Diuretics** attenuate the increased preload
- **Spirinolactone** attenuates the aldosterone-induced myocardial fibrosis.
- **Beta-Blockers** antagonize the Sympatic Nervus System and ventricular remodeling
- **ACE-Inhibitors** antagonize the Renin-Angiotensin-Aldosterone System and ventricular remodeling
- **Vasodilators** attenuate the increased afterload



ACE-I: angiotensin-converting enzyme inhibitor (captopril)
ARB: angiotensin receptor blocker (valsartan)
ARNI: angiotensin receptor-neprilysin inhibitor (sacubitril/valsartan)
Beta-blocker (carvedilol)
MRA: mineralocorticoid receptor antagonist (espironolactone)
Loop diuretic: furosemide
ICD: implantable cardioverter desfibrillator
CRT-P: cardiac resynchronization therapy pacemaker

Sympathomimetic amines
(dopamina, dobutamina)
Phosphodiesterasa Type III inhibitors
(milrinona)
Calcium sensitizer
(levosimendam)

- Ivabradine (sinoatrial node inhibitor)
- Vericiguat
- Hydralazine and isosorbide dinitrate
- Digoxin

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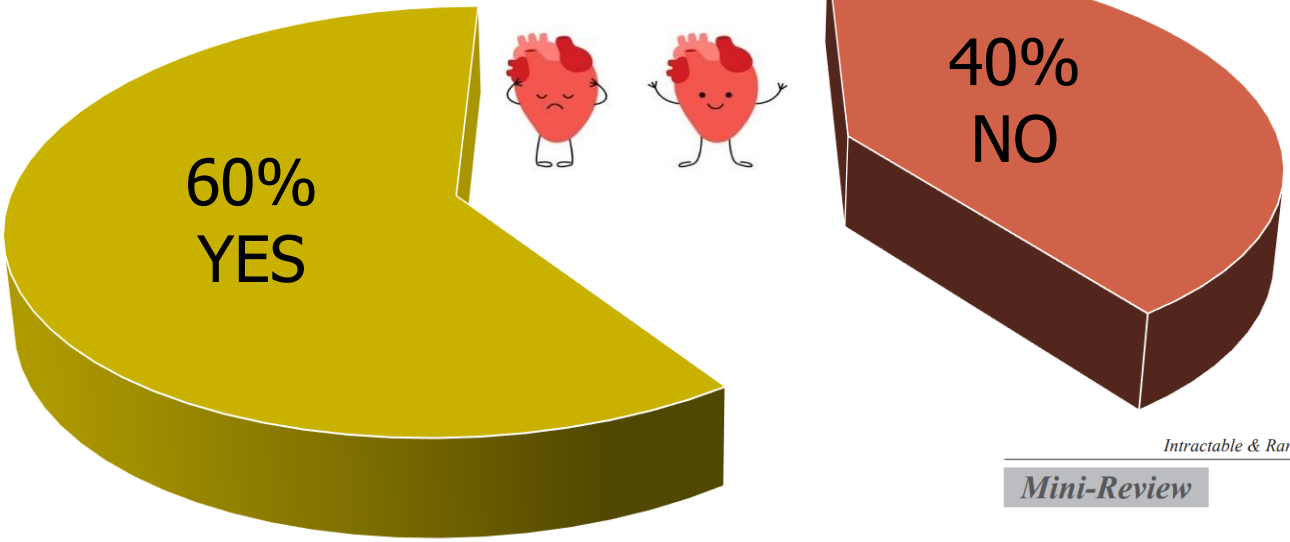
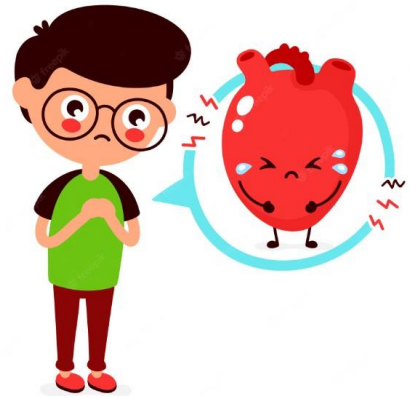
Does cardiomyopathy appear in **all patients?**

Limitations: constraints on knowledge

- Alström Syndrome is a rare condition.
- Current incidence is unknown: range from1 in 500.000 to 1 in 1.1000.000.
- Many cases remain undiagnosed.





DILATED CARDIOMYOPATHY

Intractable & Rare Diseases Research. 2021; 10(4):257-262. 257

Mini-Review

DOI: 10.5582/irdr.2021.01113

A review of Alström syndrome: a rare monogenic ciliopathy

Avijoy Roy Choudhury[1,*], Ifeanyi Munonye[2], Kevin Paul Sanu[1], Nipa Islam[3], Cecilia Gadaga[4]

[1] UWA Medical School, The University of Western Australia, Perth, WA, Australia;
[2] Uniwersytet Jagielloński Collegium Medicum, Kraków, Poland;
[3] Dhaka Medical College, Dhaka, Bangladesh;
[4] Texila American University, Georgetown, Guyana.

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Is cardiomyopathy **the same** for all patients?

The **early onset** of cardiomyopathy: Ages between 3 weeks and 4 months (42%)

Cardiomyopathy can vary, even within families

Irreversible heart failure leading to death within the first weeks of life

"Mitogenic cardiomyopathy"

Aparent recovery of cardiac function within 3 years

1 in 5 go on to

The **later onset** of cardiomyopathy: Ages between teens and late 30s (18%)

Risk of arrhythmia is not well defined

Primary endocardial fibroelastosis: neonatal presentation

Journal of Molecular Medicine (2021) 99:1623–1638
https://doi.org/10.1007/s00109-021-02112-z

JMolMed

ORIGINAL ARTICLE

Recessive ciliopathy mutations in primary endocardial fibroelastosis: a rare neonatal cardiomyopathy in a case of Alstrom syndrome

Yan Zhao[1,2,3] · Lee-kai Wang[4] · Ascia Eskin[5] · Xuedong Kang[1,2,3] · Viviana M. Fajardo[1] · Zubin Mehta[1,2,3] · Stacy Pineles[6] · Ryan J. Schmidt[7] · Aaron Nagiel[8,9] · Gary Satou[1] · Meena Garg[1] · Myke Federman[1] · Leigh C. Reardon[1,10] · Steven L. Lee[1] · Reshma Biniwale[1,11] · Wayne W. Grody[1,12] · Nancy Halnon[1] · Negar Khanlou[12] · Fabiola Quintero-Rivera[13] · Juan C. Alejos[1] · Atsushi Nakano[14] · Gregory A. Fishbein[12] · Glen S. Van Arsdell[1,11] · Stanley F. Nelson[1,4,5] · Marlin Touma[1,2,3,14,15]

- Primary **endocardial fibroelastosis** is a rare form of neonatal cardiomyopathy (1/5.000 live births).
- Deposition of sub-endocardial fibrous tissue leads to thickening of the endocardium and dilated left ventricule.
- Progressive left ventricular dysfuntion: heart failure
- Early death in 80% of cases

European Journal of Medical Genetics xxx (2014) 1–4

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Clinical research

Homozygous loss-of-function mutation in *ALMS1* causes the lethal disorder mitogenic cardiomyopathy in two siblings

Jacoba J. Louw [a,b,*], Anniek Corveleyn [b], Yaojuan Jia [b], Sajid Iqbal [b], Derize Boshoff [a], Marc Gewillig [a], Hilde Peeters [b], Philippe Moerman [c], Koenraad Devriendt [b]

[a] Department of Congenital and Pediatric Cardiology, University Hospitals Leuven, Belgium
[b] Center of Human Genetics, University Hospitals Leuven, Katholieke Universiteit Leuven, Belgium
[c] Department of Anatomical Pathology, University Hospitals Leuven, Belgium

SIBLINGS

PATIENT 1:
20 days: sudden cardio arrest and death

PATIENT 2:
Pregnancy was closely followed
Neonatal echocardiography was normal
19 days: admitted with heart failure
22 days: death

- **Mitogenic cardiomyoptahy:**

1.- An **extremely rare** type of dilated cardiomyopathy (only 8 cases have been reported in 5 families).

2.- A **lethal disorder**: irreversible heart failure leading to an death in early infancy

Transplantation Proceedings
Volume 54, Issue 10, December 2022, Pages 2800-2802

Successful Heart Transplant in Dilated Cardiomyopathy Associated With Alström Syndrome: A Case Report

Jung Min Park [a], Yu Rim Shin [c], Jae Won Oh [d], Jo Won Jung [b]

Report the case of a 17-year-old boy who underwent successful isolated heart transplant despite severe liver dysfunction

Case Reports > Pediatr Cardiol. 2013 Feb;34(2):455-8. doi: 10.1007/s00246-012-0296-6. Epub 2012 Mar 24.

Extreme clinical variability of dilated cardiomyopathy in two siblings with Alström syndrome

Jamal Mahamid [1], Avraham Lorber, Yoseph Horovitz, Stavit A Shalev, Gayle B Collin, Jürgen K Naggert, Jan D Marshall, Ronen Spiegel

Significant intra-familial variability in **two siblings**

PATIENT 1

4 weeks: heart failure
Treatment: furosemide, digoxin, captopril
3 years: recovery cardiac function, normal echocardiography

PATIENT 2

4 weeks: heart failure
Treatment: furosemide, aldacton, digoxin, captopril
3 years: dilated cardiomyopathy (furosemide, carvedilol, captopril)

AJMG AMERICAN JOURNAL OF medical genetics PART A

CLINICAL REPORT

Variable clinical course of identical twin neonates with Alström syndrome presenting coincidentally with dilated cardiomyopathy

Seth A. Hollander, Norah Alsaleh, Maura Ruzhnikov, Kristen Jensen, David N. Rosenthal, David A. Stevenson, Melanie Manning

First published: 13 April 2017 | https://doi.org/10.1002/ajmg.a.38200 | Citations: 4

Significant intra-familial variability in **two monozygotic twin infants**

TWIN 1	improved both echocardiographically and functionally
TWIN 2	showed a progressive decline in ventricular function and worsening symptoms requiring multiple hospitalizations and augmentation of heart failure therapy

Is there a **single** Alström syndrome or **different types** of the syndrome?

Hum Mutat. 2015 July ; 36(7): 660–668. doi:10.1002/humu.22796.

Alström Syndrome: Mutation spectrum of *ALMS1*

Jan D. Marshall[1,2,†,*], Jean Muller[3,4,5,*], Gayle B. Collin[1,*], Gabriella Milan[6], Stephen F. Kingsmore[7], Darrell Dinwiddie[7,8], Emily G. Farrow[7], Neil A. Miller[7], Francesca Favaretto[6], Pietro Maffei[6], Hélène Dollfus[9,10], Roberto Vettor[6], and Jürgen K. Naggert[1]

[1]The Jackson Laboratory, Bar Harbor, Maine USA

Alström syndrome is extremely complex

- Broad mutation spectrum with diverse phenotypic expressions:Genotype-Phenotype correlation?
- Presence versus abscence of cardiomyopathy?
- Significant intra-familial variability in siblings even with the same mutations?
- Multisystemic progressive affectation (lung, kidney, liver..)?
- Metabolic alterations: obesity and endocrine abnormalities (insuline resistance, type2 diabetes mellitus, dyslipidemia)?
- Enviromental or infectious exposures?

THE HEART

1.- **What** is cardiomyopathy?
2.- **Why** does cardiomyopathy appear?
3.- **When** does cardiomyopathy appear?
4.- **How** does cardiomyopathy appear?
5.- Does cardiomyopathy appear in **all patients**?
6.- Is cardiomyopathy **the same** for all patients?
7.- How does cardiomyopathy **develop**?

and what happens if…
cardiac function recovers?

but the syndrome progresses…

DEVELOPMENT OF CARDIOMYOPATHY

BIRTH

3 YEARS

ADOLESCENCE

OBESITY

TYPE 2 DIABETES

METABOLIC SYNDROME

CARDIOMYOPATHY

ASYMPTOMATIC?

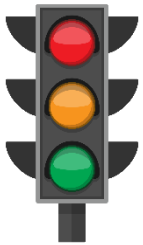
CARDIOMYOPATHY

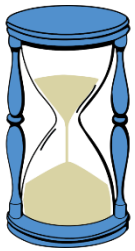
ARTERIAL HYPERTENSION

CORONARY ARTERY DISEASE

MYOCARDIAL FIBROSIS

MYOCARDIAL FIBROSIS





... TIME MATTERS.

Life expectancy is rarely over 50 years of age

DEATH

HEART FAILURE

RECOVERY

Dr. Alfonso Ortigado

Potencial role in the development of myocardial fibrosis

Obesity-hyperphagia

Raised serum Triglycerides

Insuline resistance

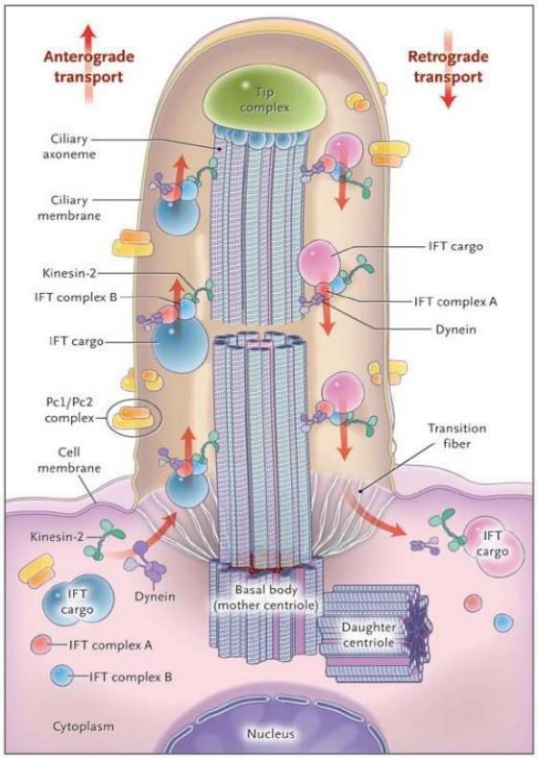
Coronary artery disease

Hypertension:
activation of the renin-angiotensin-aldosterone system

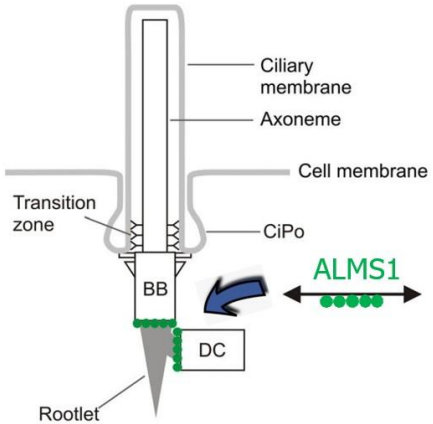
Progressive multi-organ fibroris

...is a consequence of ALMS1 dysfunction (ciliopathy) and a result of secondary metabolic alterations

Congenital component

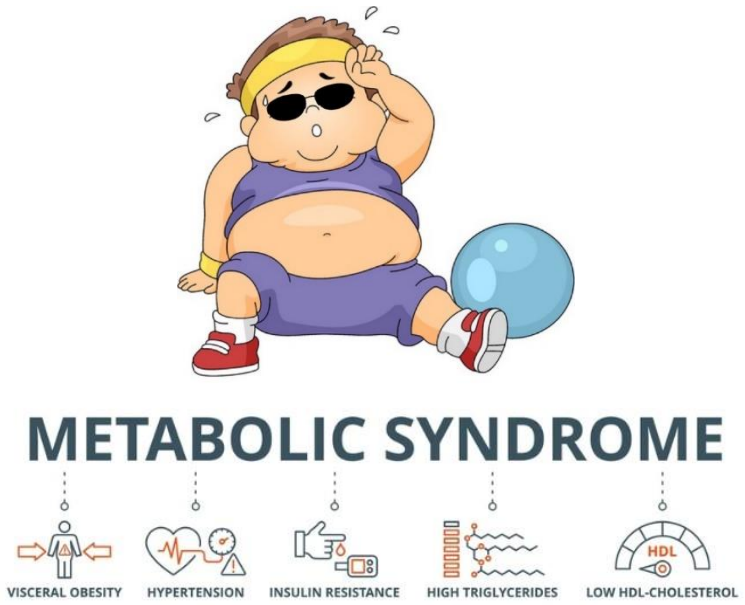


Ciliopathy



Adquired component

Obesity, HTA, Insuline resistance, dyslipidemia, coronary artery disease



Alfonso Ortigado

How can we identify myocardial fibrosis?

1.- Post-morten studies.
2.- Cardiovascular Magnetic Resonance Imaging (MRI):
- Myocardial Fibrosis: Late Gadolinium enhancement
- Difusse intersticial myocardial fibrosis: CMR T1 mapping and extracellular volumen quantification
3.- Strain Echocardiography: Global Longitudinal Strain

Cardiomyopathy: the silent progession of fibrosis

Edwards *et al. Orphanet Journal of Rare Diseases* (2015) 10:83
DOI 10.1186/s13023-015-0292-z

ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Diffuse left ventricular interstitial fibrosis is associated with sub-clinical myocardial dysfunction in Alström Syndrome: an observational study

Nicola C. Edwards[1,2*], William E. Moody[1,2], Mengshi Yuan[1], Adrian T. Warfield[3], Robert Cramb[4], Richard B. Paisey[5], Tarekegn Geberhiwot[6] and Richard P. Steeds[1,2]

Baig *et al. Orphanet Journal of Rare Diseases* (2020) 15:139
https://doi.org/10.1186/s13023-020-01426-4

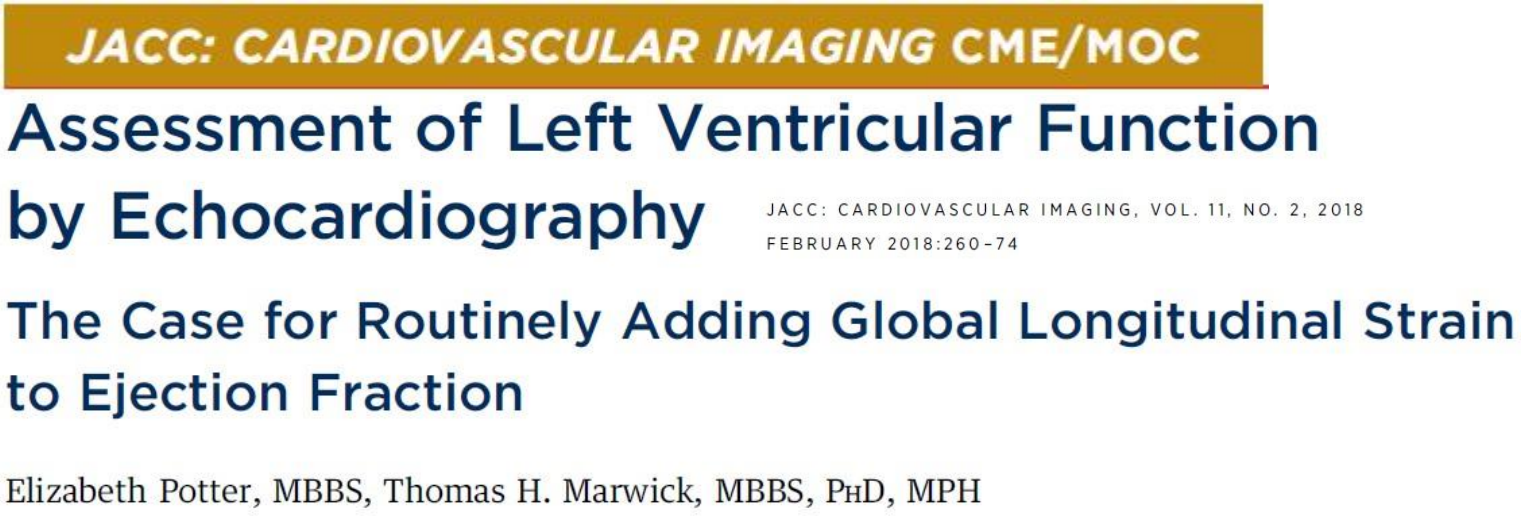
Orphanet Journal of Rare Diseases

RESEARCH Open Access

Prospective cardiovascular magnetic resonance imaging in adults with Alström syndrome: silent progression of diffuse interstitial fibrosis

Shanat Baig[1,2], Rory Dowd[3], Nicola C. Edwards[2,3], James Hodson[4], Larissa Fabritz[2,3], Ravi Vijapurapu[1,2], Boyang Liu[1,2], Tarekegn Geberhiwot[1,5] and Richard P. Steeds[2,3,6*]

Strain Echocardiography: a new opportunity



- In standar echocardiography **Left Ventricular Ejection Fraction** (LVEF) is the most frequently used parameter to asses systolic function
- Strain describes deformation of the myocardium that occurs during the cardiac cycle in the longitudinal, circumferential, and radial planes: **Global Longitudinal Strain** (GLS).
- Myocardial strain reflects changes in tissue (**fibrosis**) and detect sub-clinical myocardial dysfunction.
- Although **LVEF** will remain a cornerstone of LV function assessment, the addition of **GLS** enables detailed phenotyping and improved risk assessment and is a tool for present and future therapeutic advancement.

Management of cardiovascular risk factors

Hypertriglyceridemia
-Weight management
-Low-fat diet combined with statins and nicotic acid.
-Omega-3 fatty acids and fibrates

Insuline resistance:
-Weight management
-Insulin-sensitizing agents: metformin, thiazolidinediones (glitazones), dipeptidyl peptidase 4 inhibitors (gliptins)
-Sodium-Glucosa Transport Protein 2 inhibitors (glifozins)
-Incretin analogues or Glucagon-like peptide 1 (GLP-1) analogues

Hypertension:
-Weight management
-Angiotensin-coverting enzyme (AEC) inhibitors: captopril.
-Angiotensin II receptor blockers (ARBS): losartan

Management of cardiovascular risk factors

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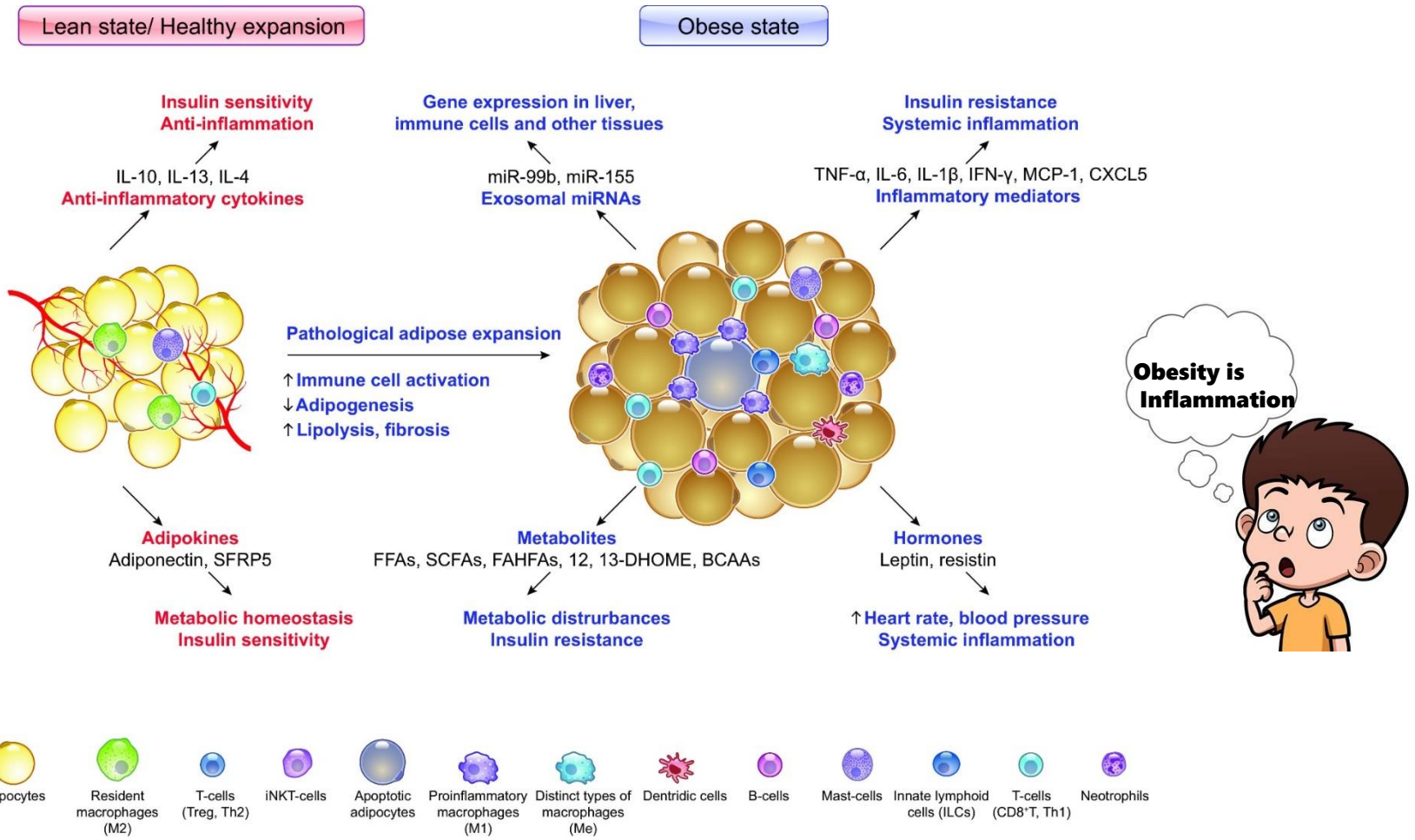
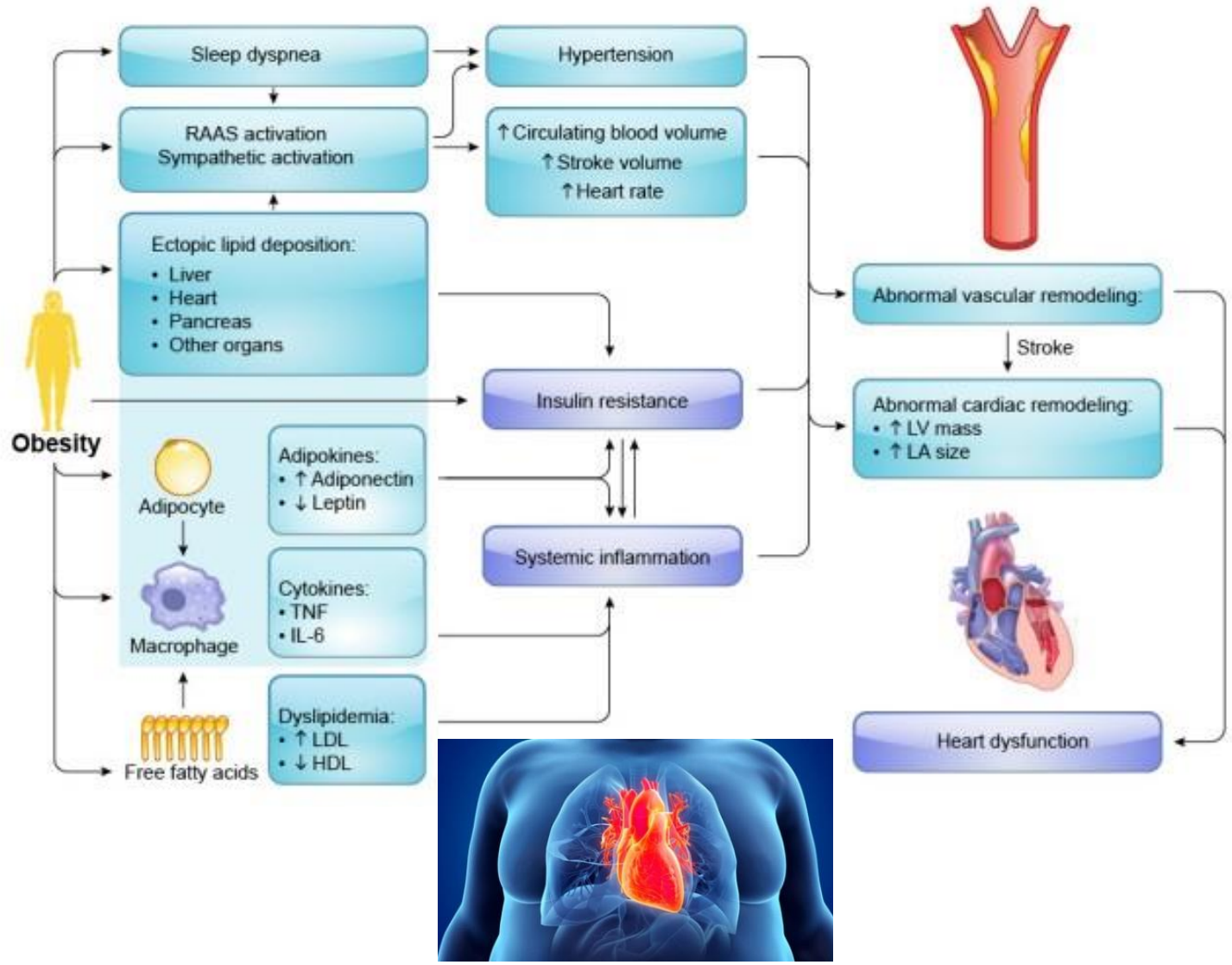
OBESITY & INFLAMMATION: "LIPOINFLAMMATION"

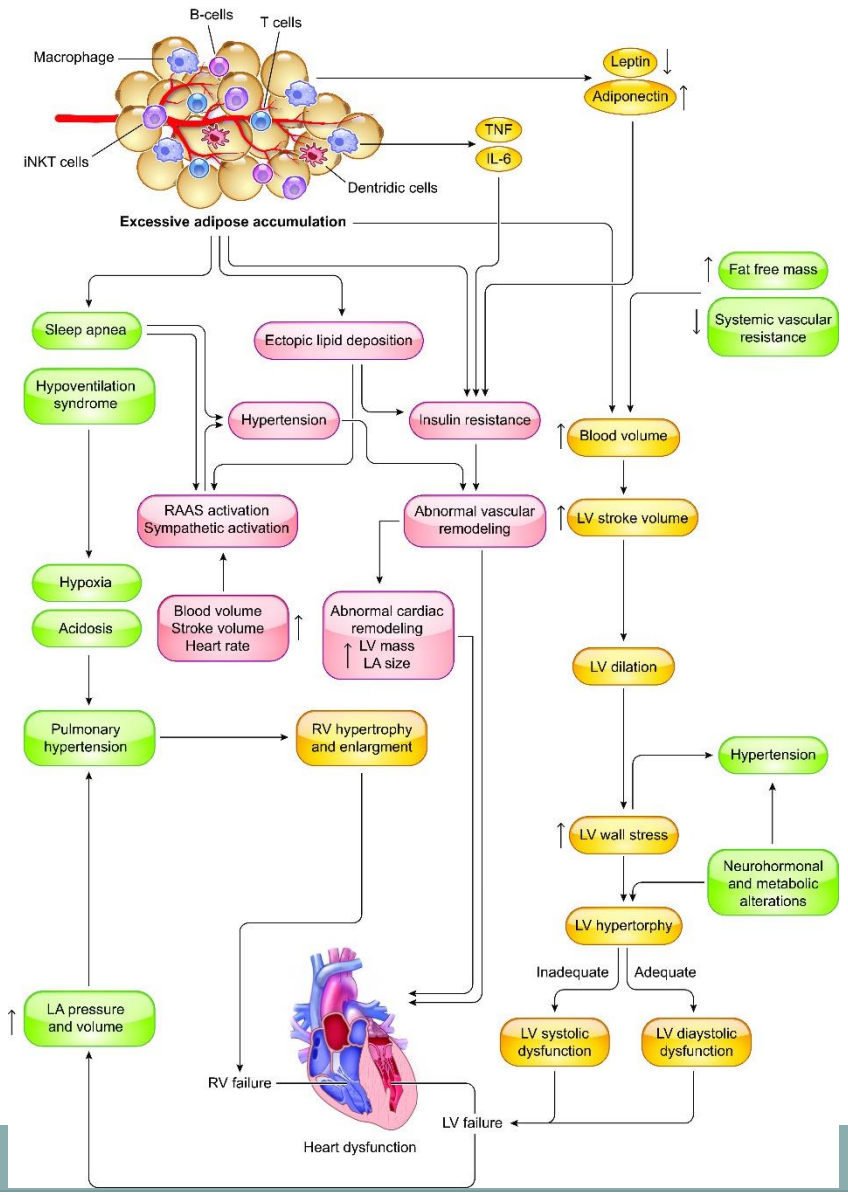


A complex process with a wide variety of cells and inflammatory mediators.

OBESITY & INFLAMMATION: "LIPOINFLAMMATION"



OBESITY & INFLAMMATION: "LIPOINFLAMMATION"



OBESITY

CHRONIC INFLAMMATION

CONSTANT THREAT

LOW-GRADE INFLAMMATION

SILENT THREAT

TREATMENT OF OBESITY: A REAL CHALLENGE

Review > Am J Manag Care. 2022 Dec;28(15 Suppl):S288-S296. doi: 10.37765/ajmc.2022.89292.

A review of current guidelines for the treatment of obesity

Marc-André Cornier [1]

Guidelines of obesity in adults

BMI,[a] (kg/m²)	Classification
18.5-24.9	Normal weight
25-29.9	Overweight
30-34.9	Class 1 obesity
35-39.9	Class 2 obesity
≥ 40	Class 3 obesity

BMI, body mass index.

1.- 2013: Guidelines by the American College os Cardiology (ACC), American Heart Asociation (AHA) and The Obesity Society (TOS).
2.- 2016: Guidelines by the American of Clinical Endocrinolist (AACE) and the American College of Endocrinology (ACE)
3.- Updates guidance: drugs and devices approved by tha FDA

Lifestyle therapy: intervention program design for weight loss.
1.- Healthy meal plan: calorie-restricted diet (carbohydrates)
2.- Physical activity presciption and reduce sedentary time
3.- Behavioral interventions

Pharmacological treatment: when is it recomended?

… EASY TO SAY, BUT HARD TO DO

-Psychosocial impact of growing up and living whith the disease.
-Psychiatric disorders: depression, ansiety.
- Hyperphagia

Calorie-restricted diet

Physical activity presciption (aerobic exercise)

-Adaptation for deaf-blind individual.
-Musculoskeletal disorders: scoliosis, kyphosis, flat foot

Pharmacological treatment: when is it recomended?

Chronic weight management in patients with a BMI of at least 27 kg/m^2 who have at least 1 weight-related complication or a BMI of at least 30 kg/ m^2

Approved Medications for the Long-Term Treatment of Obesity

1.- Orlistat.
2.- Phentermine combined with topiramate.
3.- Naltrexone combined with bupropion
4.- Liraglutide (> 12 years old).
5.- Lorcaserin
6.- Semaglutide (>18 yeas old)
7.- Setmelanotide (Bardet-Biedl syndrome, POMC, PCSK1, or LR deficiency)

Setmelanotide: a new therapy?

Clinical Trial > Lancet Diabetes Endocrinol. 2022 Dec;10(12):859-868.
doi: 10.1016/S2213-8587(22)00277-7. Epub 2022 Nov 7.

Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alström syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period

Andrea M Haqq [1], Wendy K Chung [2], Hélène Dollfus [3], Robert M Haws [4], Gabriel Á Martos-Moreno [5], Christine Poitou [6], Jack A Yanovski [7], Robert S Mittleman [8], Guojun Yuan [8], Elizabeth Forsythe [9], Karine Clément [6], Jesús Argente [10]

THE LANCET
Diabetes & Endocrinology

1.- The central hypothalamic pathway is a key regulator of energy balance.
2.- Pathway disruption leading to impaired melanocarin-4 receptor (MC4R) contributes to hyperpagia
3.- Setmelanotide is a MC4R agonist and can restore MC4R signalling
4.- Setmelanotide reduces bodyweight and hunger in patients with Bardet-Biedl syndrome.
5.- The effects of setmelanotide in Alström syndrome were inconclusive and require further exploration

Research and Development: is our future

Baig *et al. BMC Endocrine Disorders* (2018) 18:88
https://doi.org/10.1186/s12902-018-0315-6

BMC Endocrine Disorders

STUDY PROTOCOL Open Access

Treatment with PBI-4050 in patients with Alström syndrome: study protocol for a phase 2, single-Centre, single-arm, open-label trial

Shanat Baig[1,2], Vishy Veeranna[1], Shaun Bolton[1], Nicola Edwards[2,3], Jeremy W. Tomlinson[4], Konstantinos Manolopoulos[5], John Moran[6], Richard P. Steeds[2,3] and Tarekegn Geberhiwot[1,5,7*]

Clinical features of ALMS	Corresponding pre-clinical effects of PBI-4050
Loss of organ function due to fibrosis involving	
Heart	↓ heart fibrosis in suprarenal aortic banding in rats
Lung	↓ lung fibrosis in bleomycin-induced lung fibrosis in mice
Liver	↓ liver fibrosis in CCl4-induced liver fibrosis in rats
Kidneys (renal failure)	↓ kidney fibrosis in various animal models of kidney fibrosis
Type 2 diabetes mellitus	
Early hyperinsulinemia	Reduces insulin resistance in db/db diabetic mice and db/db eNOS−/− diabetic mice
Severe insulin resistance	Normalizes glycaemia in diabetic mice
Late pancreatic failure	Maintains (early treatment) or restores (late treatment) insulin content in pancreatic islets

eNOS$^{-/-}$ endothelial nitric oxide synthase knockout (mice)

1.- PBI-4050 is a 3-pentylbenzeneacetic acid sodium salt with a molecular weight of 228.3.
2.- PBI-4050 is a new molecular entity with demonstrated anti-inflammatory and anti-fibrotic activities in both in vitro and in vivo models.
3.- PBI-4050 is a potential drug candidate for the treatment of inflammatory and fibrosis-related diseases.

Semaglutide: beyond good glycemic control

frontiers in Endocrinology

REVIEW
published: 25 June 2021
doi: 10.3389/fendo.2021.645617

Efficacy of Semaglutide in a Subcutaneous and an Oral Formulation

Juris J. Meier *

Diabetes Center Bochum-Hattingen, St. Josef-Hospital, Ruhr-University Bochum, Bochum, Germany

EXPERIMENTAL AND THERAPEUTIC MEDICINE 20: 2396-2400, 2020

Metabolic and cardiovascular benefits of GLP-1 agonists, besides the hypoglycemic effect (Review)

ROUA ANAMARIA IORGA[1], NICOLAE BACALBASA[2], MARA CARSOTE[3], OVIDIU GABRIEL BRATU[4,5], ANA MARIA ALEXANDRA STANESCU[6], SIMONA BUNGAU[7], CARMEN PANTIS[8] and CAMELIA CRISTINA DIACONU[9]

1.- Semaglutide is a glucagon like peptide-1 (GLP-1) receptor agonist.
2.- Semaglutide activates the receptor of the gut-derived hormone GLP-1.
3.- Hormone GLP-1 has an important role in glucose homeostasis.
4.- Semaglutide is much more than a glucose-lowering agent (low risk of hypoglycemia)

1.- Stimulate insulin secretion
2.- Reduce glucagon release.
3.- Reduce hepatic glucose output (suppressed hepatic gluconeogenesis
4.- Delay gastric emptying
5.- Increase satiety (reduce appetite and energy intake)
6.- Improve cardiovascular risk factors.

GLP-1RAs: improve cardiovascular risk factors

1.- Type 2 Diabetes: better glucose homeostasis.
2.- Obesity: reducing appetite and energy intake, reducing body weight
3.- Hypertension: inhibition of the renin-angiotensin-aldosterone system, improvement of endothelial function and direct activation of specific receptors in the vascular tissue.
4.- Atherosclerosis: regulating multiple inflammatory pathways in proatherogenic apolipoprotein E-deficient mice and low-density lipoprotein receptor deficient mice.
5.- Myocardial fibrosis: control of inflammatory pathways in obesity (lipoinflammation).
6.- Cardioprotective effect: reducing apoptosis in cardiac cells of rats.

Reviews in Endocrine and Metabolic Disorders (2022) 23:521–539
https://doi.org/10.1007/s11154-021-09699-1

Semaglutide, a glucagon like peptide-1 receptor agonist with cardiovascular benefits for management of type 2 diabetes

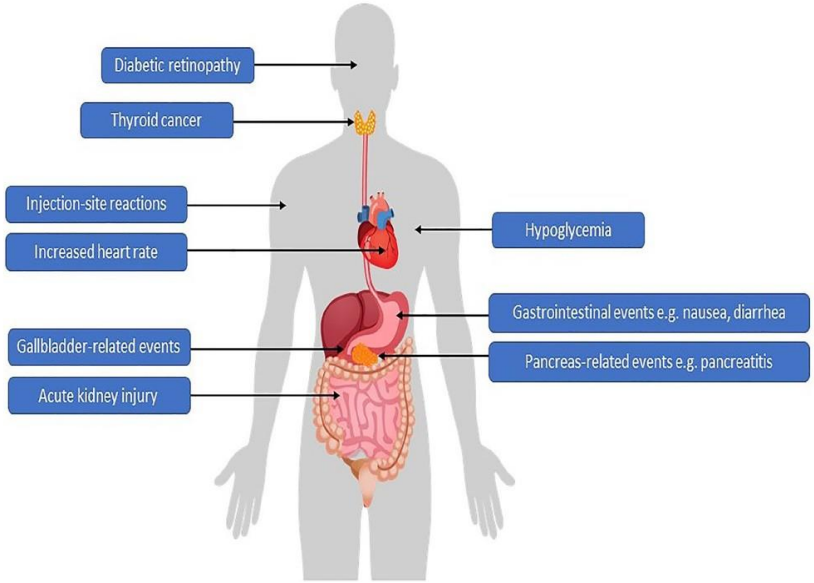
Manoj Kumar Mahapatra[1] · Muthukumar Karuppasamy[2] · Biswa Mohan Sahoo[3]

Semaglutide: adverse events

1.- **Hypoglycemia** (low risk if monotherapy
2.- **Gastrointesinal**-related events (most commom):
- Nausea-vomiting: mild to moderate in intensity, and transient
- Constipation-diarrhea
- Abdominal pain
3.- **Diabetic retinopathy**: blindness, vitreous haemorrhage, necessity of photocoagulation, and use of intravitreal agents)
4.- **Heart**: increase heart rate, no effect on QT interval
5.- **Others:** pancreatitis, cholecystitis, acute kidney injury?,injection-site reactions.

Before using semaglutide you should check:
Renal and pancreatic function

Do not use semaglutide if:
1.- You or any of your family have ever had medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2.
2.- You are allergic to semaglutide or any of the ingredients



Semaglutide: available as both subcutaneous injection and as an oral formulation

Effective reductions in blood glucose, HbA_{1c}, and body weight

Subcutaneous semaglutide

Oral semaglutide

Once-weekly administration by injection

May be convenient for patients:
- Taking multiple medications
- Frequent travelers
- Easy-to-use prefilled pen device

Dosing instructions
- None

Storage
- Requires refrigeration

Adherence
- May be improved adherence with once-weekly versus more frequent dosing

Cost
- Consider cost-effectiveness compared with other available treatments in specific setting and healthcare system
- Formulary/reimbursement factors

Once-daily administration by tablet
- May benefit patients with concerns about injectables (e.g., fear of needle pain, concerns about injecting correctly, and side effects etc.)

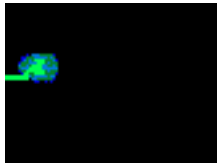
Dosing instructions
- Need to follow specific instructions daily

Storage
- No refrigeration required
- Should be stored in blister packs

Adherence
- May be improved versus injectables
- Dosing conditions must be acceptable

Cost
- Consider cost-effectiveness compared with other available treatments in specific setting and healthcare system
- Formulary/reimbursement factors

Tahani *et al. Orphanet Journal of Rare Diseases* (2020) 15:253
https://doi.org/10.1186/s13023-020-01468-8



Orphanet Journal of Rare Diseases

POSITION STATEMENT Open Access

Consensus clinical management guidelines for Alström syndrome

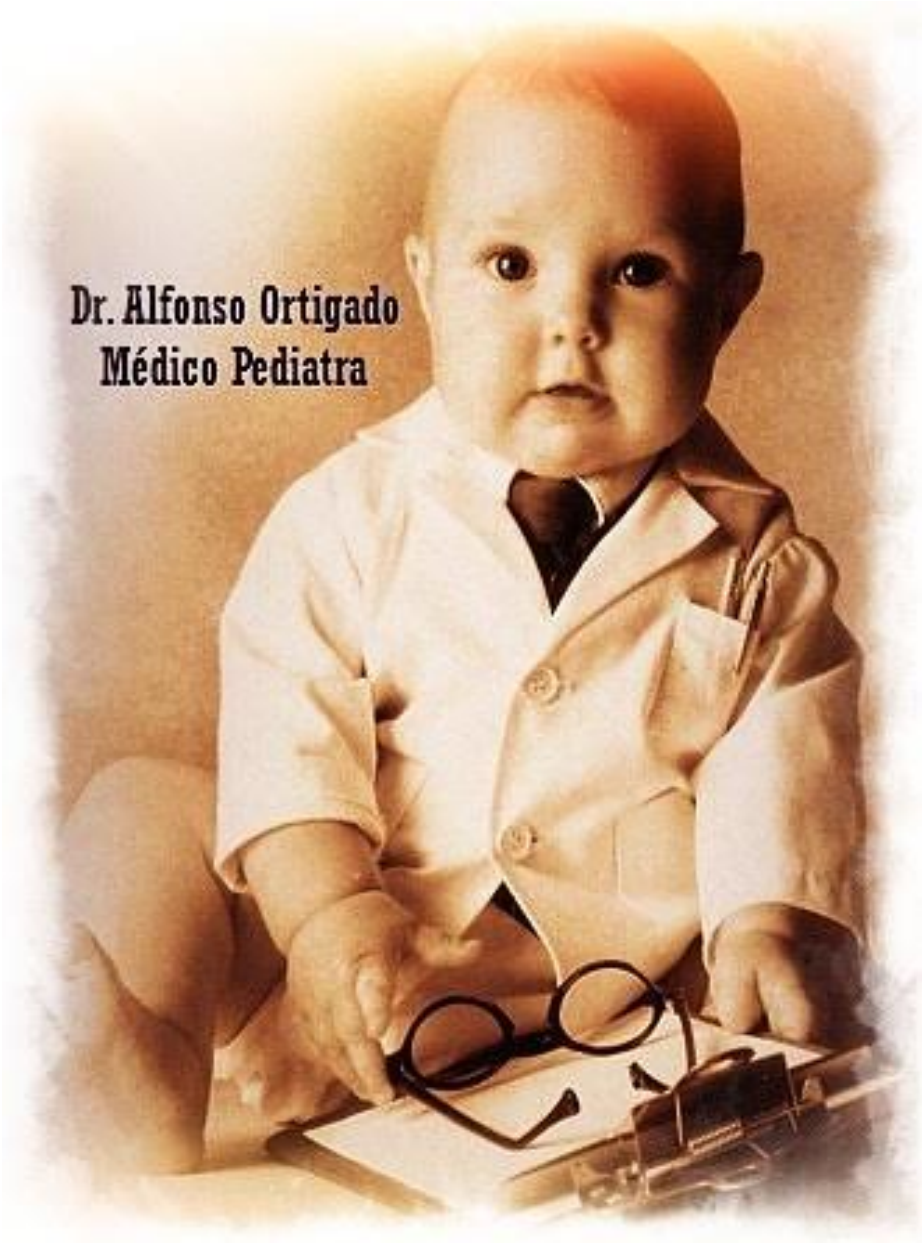
Natascia Tahani[1], Pietro Maffei[2,3], Hélène Dollfus[4,5], Richard Paisey[6], Diana Valverde[7], Gabriella Milan[2], Joan C. Han[8], Francesca Favaretto[2], Shyam C. Madathil[9], Charlotte Dawson[1], Matthew J. Armstrong[10], Adrian T. Warfield[11], Selma Düzenli[12], Clair A. Francomano[13], Meral Gunay-Aygun[14], Francesca Dassie[2], Vincent Marion[5], Marina Valenti[15,16], Kerry Leeson-Beevers[17], Ann Chivers[17], Richard Steeds[18], Timothy Barrett[19] and Tarekegn Geberhiwot[1,20*]

- Standard 12-leads **electrocardiograma** (ECG): yearly.
- **Echocardiogram**: yearly or as per clinical need.
- **Cardiac Magnetic Resonance** (CMR) (older children and adult): 3 to 5 yearly intervals (strain echocardiography?)
- **Metabolic control** (blood glucose, HbA1c, lipid profile): every 6-12 months

Learning points discussions

1.- Alström syndrom is a complex, inherit, multisystemic and progressive disease (requires a multidisciplinary team)
2.- Infants and young children who debut with dilated cardiomyopathy should be examined for syndromic features of Alström syndrome, specially eyes (nystagmus, photophobia).
3.- Strain echocardiography suggests that some degree of myocardial fibrosis is propably present in almost all patients with Alström syndrom including asymptomatic children.
4.- Time matters: between the early (infants) and the later (adults) onset of cardiomyopathy even in asymptomatic patients (progressive fibrosis).
5.- Alström syndrom is not yet curable but is a treatable condition for the development of cardiomyopathy in adults (treating obesity, metabolic disordes, hypertension).


You are not alone!



Thank you!

Alfonso Ortigado

ALSTRÖM SYNDROME INTERNATIONAL

ASI