Malattie mitocondriali con interessamento cardiaco: cosa deve sapere il cardiologo clinico?

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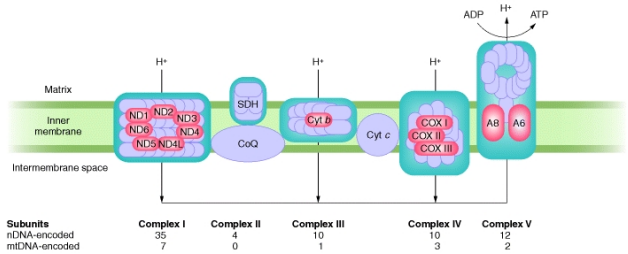
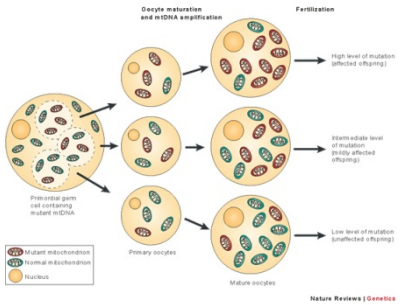
primary mitochondrial disorders
-> respiratory chain defects



Complicated disorders with myriad signs and symptoms and body systems involved (all tissues may be affected except red blood cells)

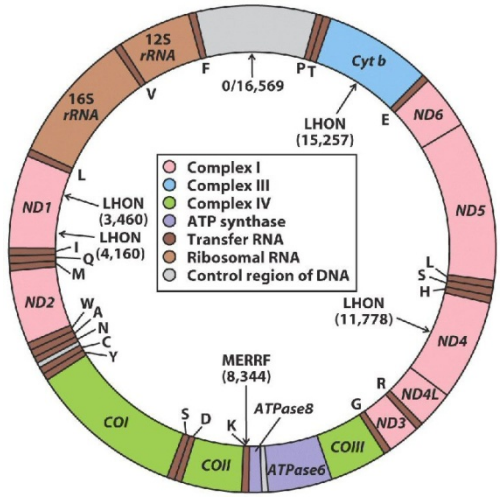
dual genomic contribution in the assembly of mitochondrial respiratory complexes

>1500 mitocondrial proteins; only 13 encoded by mtDNA



• maternal inheritance

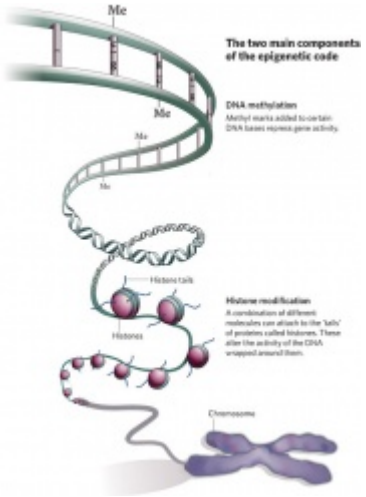
PEO/KSS
MELAS
MERRF



- mtDNA single deletion (sporadic)
- mtDNA point mutations (maternal)

cross-talk

- mtDNA multiple deletion
- mtDNA depletion



mendelian

normal mtDNA

Leigh syndrome

Cardiac involvement in primary mitochondrial disease

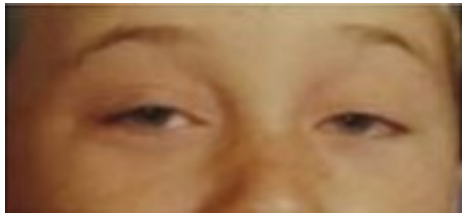
Common, often part of a multisystem mitochondrial disorders and can include both conduction abnormalities and/or cardiomyopathy

- ➢heart block frequently present in patients with large-scale mtDNA deletions
- ➢WPW and ventricular preexcitation in m.3243A>G / m.8344A>G
- ➢hypertrophic cardiomyopathy (HCM) in patients with mtDNA point mutations (m.3243A>G / m.8344A>G and others)
- dilated cardiomyopathy, less frequent than HCM and can occur as a progression from HCM, with a dilated and hypokinetic LV
- rare: restrictive cardiomyopathy and histiocytoid cardiomyopathy

mitochondrial diseases associated with single sporadic mtDNA deletions

sporadic

- **KSS**



Onset<20 yr
PEO
Pigmentary retinopathy
Diabetes
>>>Heart block >>>PaceMaker
sensorineural hearing loss
Cerebellar ataxia
CSF protein >100mg/L
Short stature

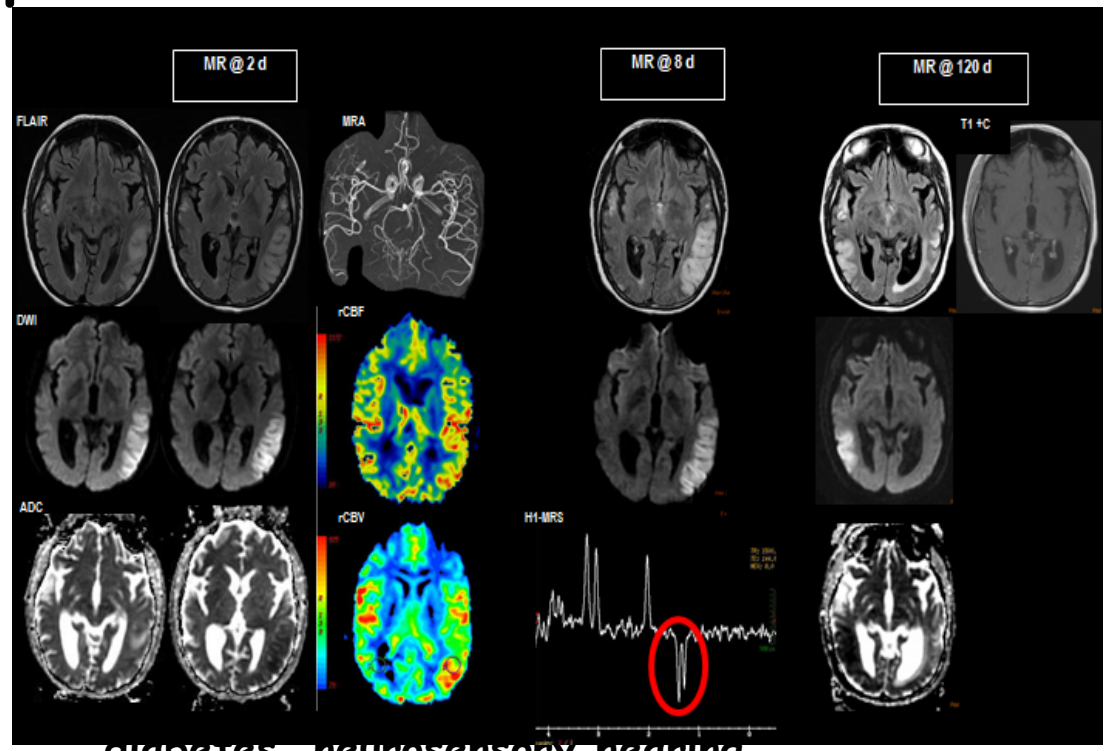
- isolated atrioventricular block
- right and left bundle branch blocks
- complete AVB requiring pacemaker implantation

often progress unpredictably to complete AVB,frequently cause of sudden death

- **PEO**

Ptosis
Ophthalmoplegia
Proximal weakness

MELAS - Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like epidodes



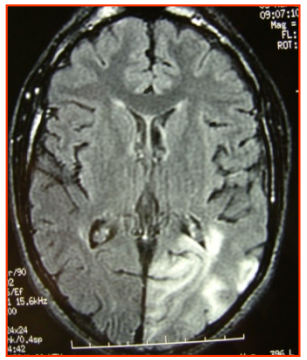
Most common CNS clinical manifestations

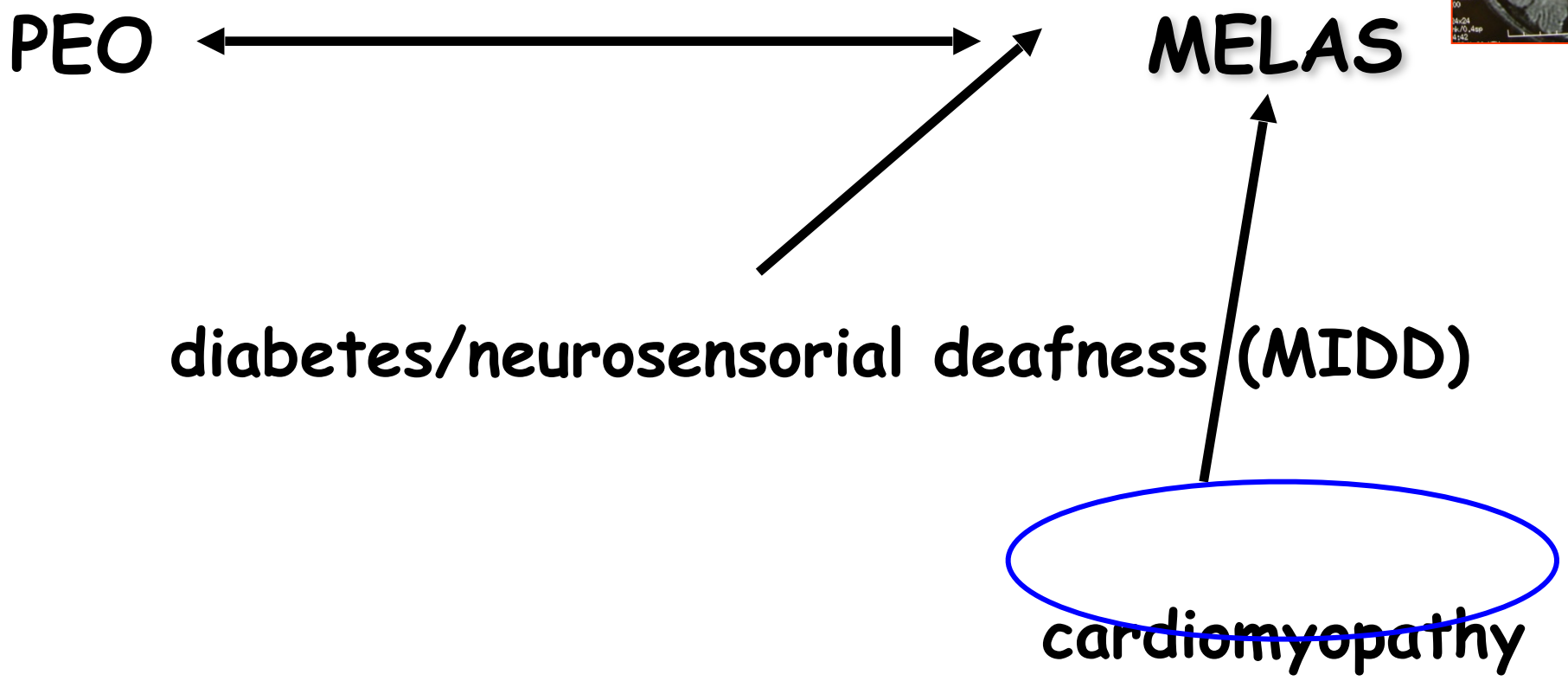
- Stroke-like episodes (SLEs) (>90%)
- Epilepsy (71-96%)
- Cognitive and psychiatric problems
- Migraine (54-91%)

Multisystem disorder (PEO/myopathy, diabetes, neurosensory hearing loss, **hypertrophic cardiomyopathy** (LVH reported in 38–56% of patients, gastrointestinal dysmotility…)

➢**Most common genetic defect**: **m.3243A>G** (2/3)

- m.3243A>G – associated phenotypes
- only 30% have the classical MELAS phenotype; rest of the patients: MIDD, MELAS/MIDD; PEO; MIDD/CPEO; MELAS/CPEO; cardiomyopathy; other…..





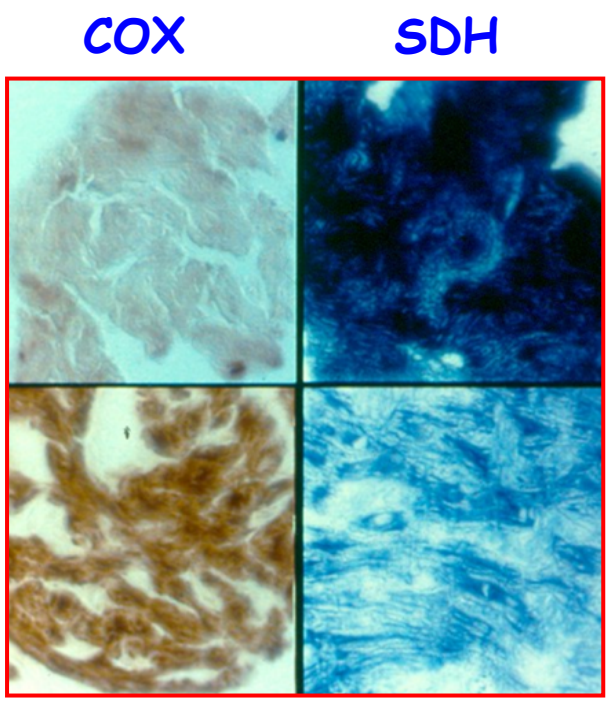
m.3243A>G PEO + cardiomyopathy

COX

muscle (het. 82%)

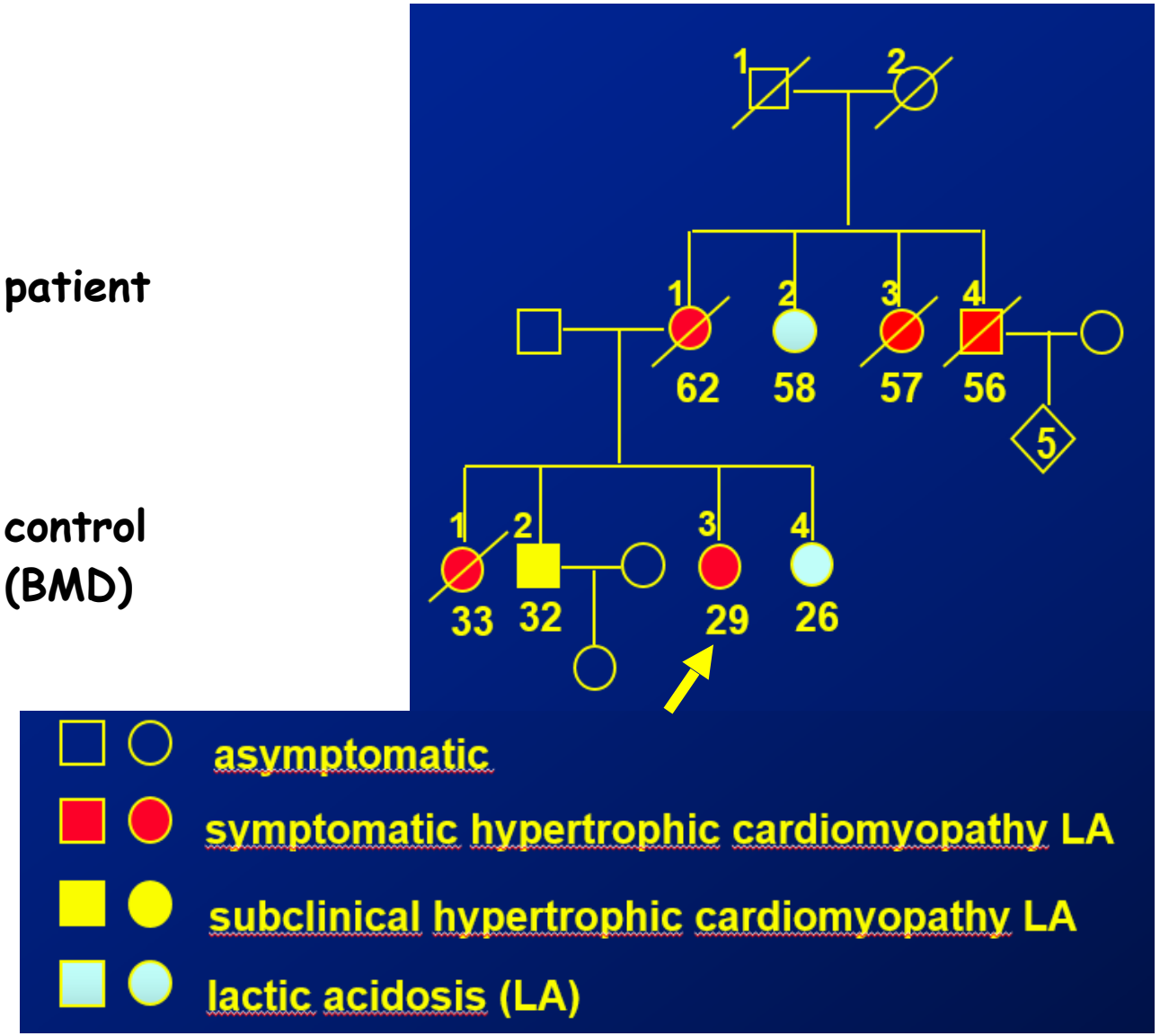
heart (het. 75%)

m.3243A>G maternally inherited cardiomyopathy



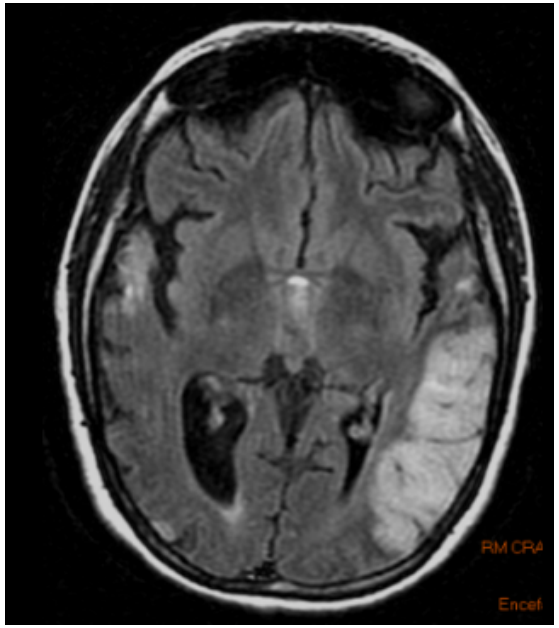
patient

control
(BMD)



heteroplasmy
muscle 91%, heart 94%,
blood 50%

Young woman diagnosed with MELAS at the age of 21, with mild cognitive impairment, SLEs, seizures, but normal cardiac function. At the age of 23 dyspnea and rapidly progressive intractable heart failure requiring ICU. The echocardiogram demonstrated left ventricle of normal volumes and normal thicknesses with hyperechoic walls with significant contractile dysfunction due to global hypokinesia; normal sized right ventricle with significant contractile dysfunction due to reduced longitudinal and radial kinesis.
The heart biopsy excluded nyocarditis and showed marked mitochondrial abnormalities.
She died within 15 days due to cardiogenic shock and severe metabolic acidosis.



Severe, rapidly progressive heart failure in MELAS

European Heart Journal (2016) **37**, 2552–2559
doi:10.1093/eurheartj/ehv306

BASIC SCIENCE

Sudden adult death syndrome in m.3243A>G-related mitochondrial disease: an unrecognized clinical entity in young, asymptomatic adults

Yi Shiau Ng[1], John P. Grady[1], Nichola Z. Lax[1], John P. Bourke[2], Charlotte L. Alston[1], Steven A. Hardy[1], Gavin Falkous[1], Andrew G. Schaefer[1], Aleksandar Radunovic[3], Saidi A. Mohiddin[4], Matilda Ralph[5], Ali Alhakim[6], Robert W. Taylor[1], Robert McFarland[1], Douglass M. Turnbull[1], and Gráinne S. Gorman[1]*

- Systematic review of cause of death in 209 m.3243A>G patients cohort allowed to estimate an incidence incidence of sudden adult death is 2.4 per 1000 person-years.
- SADS is an important cause of death in patients with m.3243A.G and likely to be due to widespread respiratory chain deficiency in cardiac muscle. The involvement of asymptomatic relatives highlights the importance of family tracing in patients with m.3243A.G and the need for specific cardiac arrhythmia surveillance in the management of this common genetic disease.

J Neurol (2015) 262:701–710
DOI 10.1007/s00415-014-7632-0

ORIGINAL COMMUNICATION

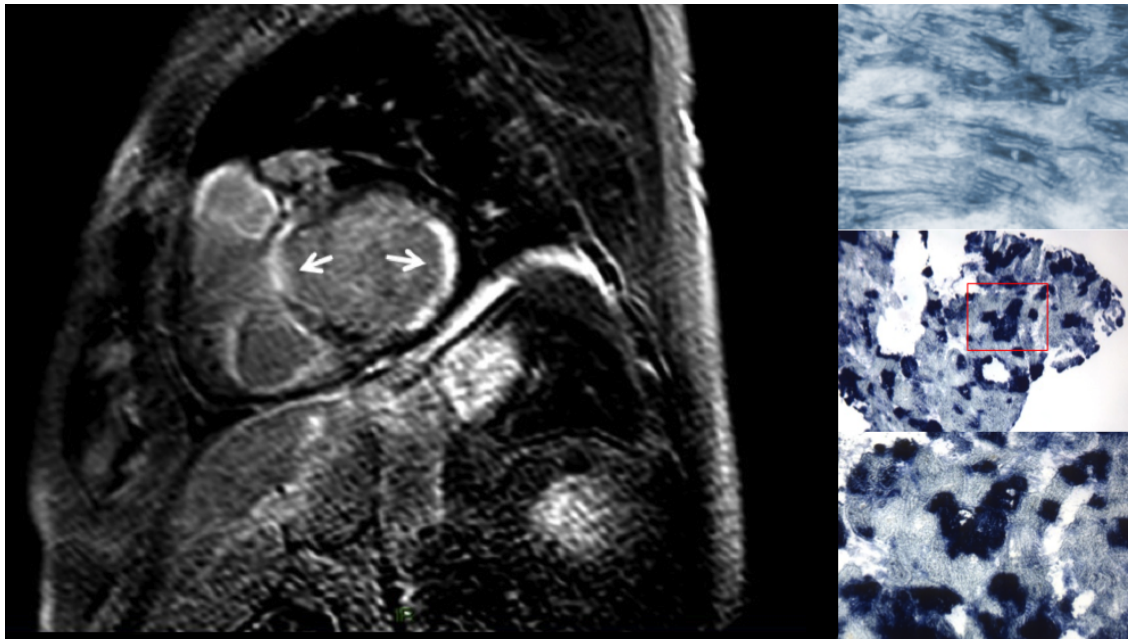
"Myo-cardiomyopathy" is commonly associated with the A8344G "MERRF" mutation

Michela Catteruccia · Donato Sauchelli · Giacomo Della Marca · Guido Primiano · Cristina Cuccagna · Daniela Bernardo · Milena Leo · Antonella Camporeale · Tommaso Sanna · Alessandro Cianfoni · Serenella Servidei

Frequency of main clinical features in 15 MERFF patients: exercise intolerance and/or muscle weakness 67 %, respiratory involvement 67 %, lactic acidosis 67 %, cardiac abnormalities 53 % (40% had also cardiac dysrhythmias), peripheral neuropathy 47 %, myoclonus 40 %, epilepsy 40 %, ataxia 13 %. A restrictive respiratory insufficiency requiring ventilatory support was observed in about half of our patients (47%). One patient developed a severe and rapidly progressive cardiomyopathy requiring cardioverter-defibrillator implantation.

Severe progressive hypertrophic cardiomyopathy in MERFF

A 55-year-old man within 2 years developed significant dilatation and dysfunction of the left ventricle with global hypokinesia and severe systolic dysfunction (EF 33 %), despite appropriate therapy with ACE inhibitors, beta-blockers, furosemide and spironolactone.
Cardiac MRI confirmed the global hypokinesia of the left ventricle (EF 28%) and a depressed global systolic dysfunction of the right ventricle (EF 38%).
The presence of mitochondrial abnormalities at the heart biopsy confirmed the mitochondrial origin of the cardiomyopathy.
He was implanted with implantable cardioverter-defibrillator at the age of



Cardiac MRI -> diffuse intramural LGE and global hypokinesia of the left ventricle (EF 28%) and depressed global systolic dysfunction of the right ventricle (EF 38%).

m.8344A>G mutation heteroplasmy
muscle 78%, heart 85%, blood 65%

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ORIGINAL INVESTIGATIONS

Cardiac Outcomes in Adults With Mitochondrial Diseases

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- The authors analyzed outcome to develop risk stratification based on independent factors for Heart Failure (HF) and arrhythmic major adverse cardiac events (MACE).
- About 38% of the cohort of 600 patients with molecular diagnoses of mitochondrial disease exhibited cardiac involvement at baseline,
- The most common molecular findings were MT-TL1 m.3243A>G variant in 208 patients and single large-scalemtDNA deletions in 171 patients.
- The multivariable predictors of HF were: MT-TL1 m.3243A>G variant, conduction defects, left ventricular hypertrophy, left ventricular ejection fraction <50%, and premature ventricular beats at baseline.
- Arrhythmic MACE predictors were single large-scale mtDNA deletions, conduction defects, and left ventricular ejection fraction <50%.

➢ The risk for arrhythmic MACE was high in patients with single large-scale mtDNA deletions

➢ Hypertrophic cardiomyopathy was the most common phenotype

➢ Cardiac magnetic resonance may further increase suspicion of an underlying mitochondrial etiology

Cardiac involvement in primary mitochondrial disease

common and can include both conduction abnormalities and cardiomyopathy

- ➢heart block frequently present in patients with large-scale mtDNA deletions
- ➢WPW and ventricular preexcitation in m.3243A>G / m.8344A>G
- ➢hypertrophic cardiomyopathy in patients with mtDNA point mutations (m.3243A>G / m.8344A>G and others)
- pacemaker implantation in atrio-ventricular block may prevent sudden cardiac death
- ACE inhibitors may prevent early hypertrophic remodelling
- beta blockers or calcium channel blockers can help the heart in pathological hypertrophy by slowing heart rate
- implantable cardioverter-defibrillator if needed
- if severe cardiomyopathy dominates the phenotype and the other organs are relatively spared, heart transplantation maybe an option

Cardiac involvement in primary mitochondrial diseases

All patients should have

cardiovascular assessment

- ECG, trans-thoracic echocardiogram, Holter (24-hour) at diagnosis and repeated annually or even less in high-risk patients
- cardiac MRI in all patients with inadequate or abnormal echocardiographic images
- longer term monitoring, including implantable loop recorders, in all patients with very frequent paroxysmal symptoms suggestive of cardiac involvement

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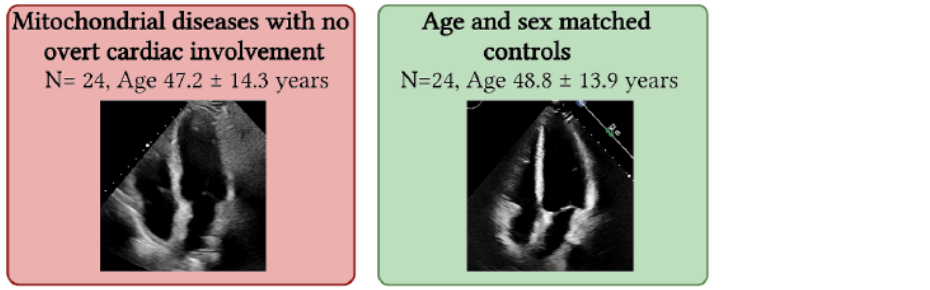
Short communication

Early cardiac mechanics abnormalities in patients with mitochondrial diseases

Rosa Lillo [a,b,1], Maria Chiara Meucci [a,1], Silvia Malara [b], Guido Primiano [c], Serenella Servidei [c,d], Antonella Lombardo [a,b], Maria Grandinetti [a], Massimo Massetti [a,b], Gaetano Antonio Lanza [a,b], Giuseppe Limongelli [e], Francesca Graziani [a,*]



24 MDs patients (50 % males, mean age 47.2 ± 14.3 years).
Most prevalent mutation was the MT-TL1 m.3243A>G (37.5 %).
In MDs patients all dimensional echocardiographic parameters were similar to controls.
Tissue Doppler septal systolic (p = 0.002) and early diastolic velocities (p = 0.016) were significantly lower and E/e' ratio was higher (p = 0.032) in MDs. Moreover, LV-GLS was significantly reduced in MDs as compared to their counterparties (20.2 ± 1.6 vs 22.6 ± 1.5, p < 0.001). Similarly, LA reservoir and conduit strain were significantly lower in MDs (31.7 ± 7.0 vs 35.9 ± 6.6, p = 0.038; 19.7 ± 5.6 vs 23.1 ± 6.0, p = 0.049 respectively), while LA contractile strain was similar between the two groups. Lower values of LV-GLS were observed in patients with NMDAS > 21 vs patients with NMDAS ≤ 21 (19.0 ± 1.2 vs 21.0 ± 1.3, p = 0.001)
Conclusion: in patients with MDs and no overt cardiomyopathy, tissue doppler and speckle tracking

Conclusion

Red flag for suspecting a mitochondrial diseases in a heart patient

- non mendelian maternal transmission
- multisystem disorders
- presence of PEO and/or sensorineural hearing loss and/or short stature and/or diabetes
- history of SLEs

What are the risks for a mitochondrial heart patient?

- risk of unpredictably atrioventricular block
- risk of sudden death
- risk of rapid deterioration of cardiac involvement induced by metabolic crisis

➢The best cure is prevention -> early screening and adeguate follow-up may provide significant benefits in terms of morbidity, mortality, and quality of life

THANK YOU