ROLE OF MICRORNAs AND MUSCLE IMAGING IN LIPID STORAGE MYOPATHIES

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Introduction:

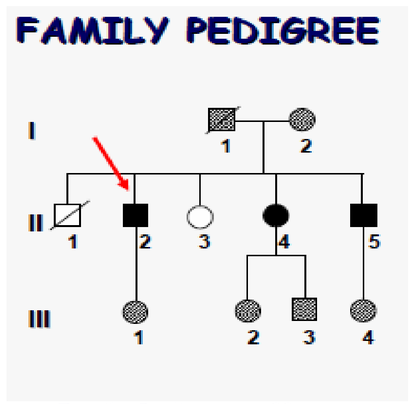
Neutral lipid storage disease with myopathy (NLSD) is a rare autosomal recessive disorder caused by mutation in the PNPLA2 gene, encoding an adipose triglyceride lipase (ATGL), containing an N-terminal patatin-like domain that is common in many acyl-hydrolases. The protein has 88% homology to mouse desnutrin. NLSD-M is characterized by an accumulation of triglycerides into cytoplasmic lipid droplets. About 30 cases are reported in the literature, mostly with progressive muscle weakness involving both proximal and distal limb muscles. NLSD-M patients are mainly affected by myopathy, cardiomyopathy and hepatomegaly, but clinical severity is highly variable.

MicroRNA (miRNA) are single stranded non-coding RNA which function is post-transcriptional regulation of target mRNA of multiple genes. MiR-1, miR-206, miR-133a are increased in serum of DMD, BMD, LGMD, suggesting their role in muscle regeneration. MiRNA are stable with exercise at difference with CK.

Methods:

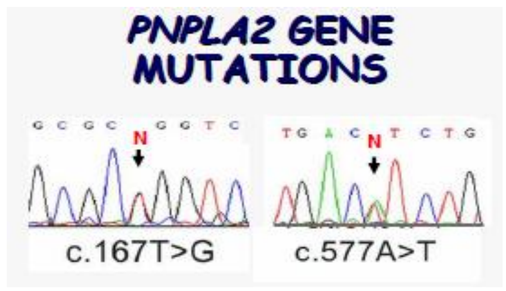
Patients: We studied a family of 4 members in which the severity of clinical features were higly variable. In two male siblings aged 61 and 50 there was an asymmetric distal myopathy, while in a 58 years old woman hepatosteatosis, diabetes were the main signs, they have two heterozygous ATGL mutations

Three family member and one carrier were studied: three muscle biopsieses were done, in two male siblings. In the 61 years old man a muscle imaging by Whole body CT was done, while the 50 year old brother was subjected on MRI.
We studied the expression of **muscle-specific miRNA** (myo-miRNA) in serum of 4 family members with NLSD-M

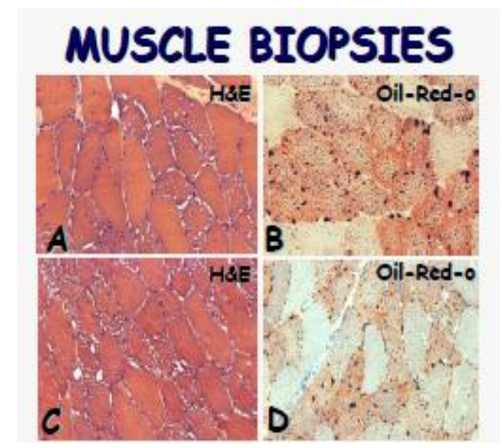


Family Pedigree: affected patients are showed in black

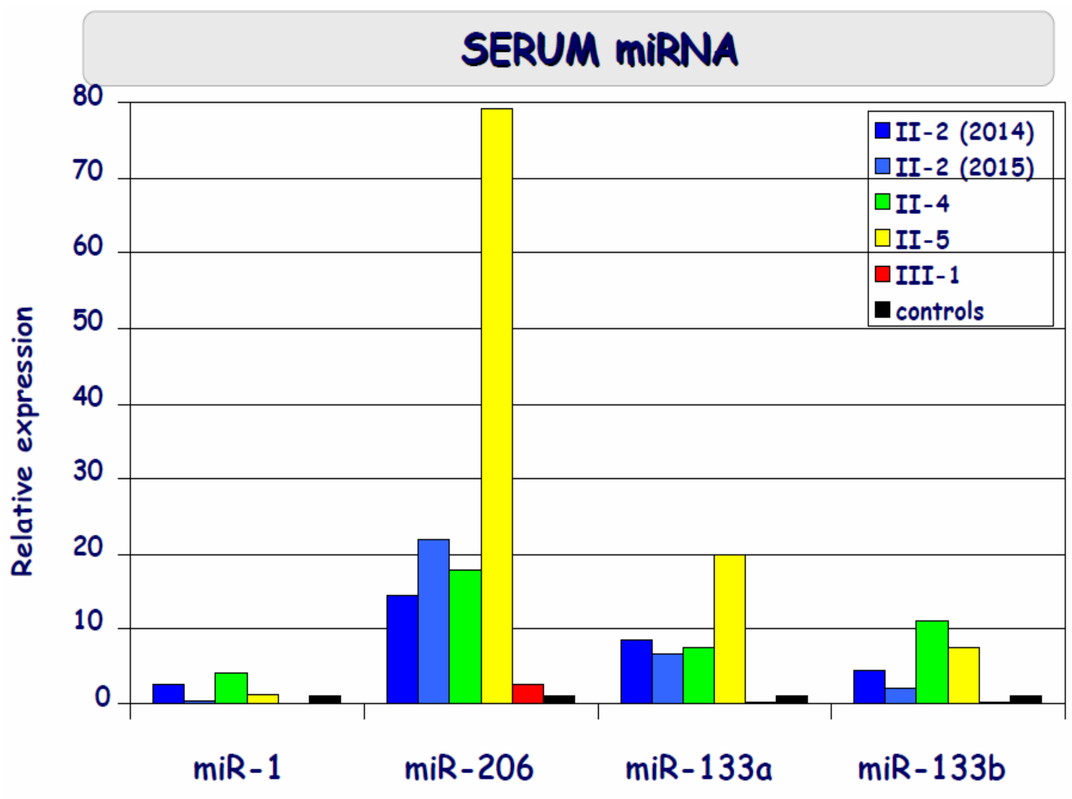
Blood amear showed Jordan's anomaly (lipid droplets) in leukocytes from Pt. II-2



DNA sequencing showed 2 compound heterozygous mutations in PNPLA2 gene: c.167T>G, p.L56R in exon 2, and c.577A>T, p.I193F in exon 5.

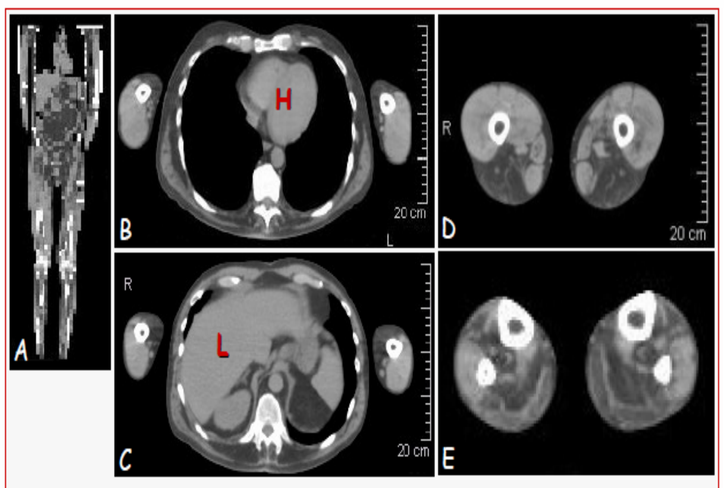


Muscle biopsy from Pt. II-2 (A,B) and PT. II-5 (C,D) showed vacuoles filled with lipid droplets.



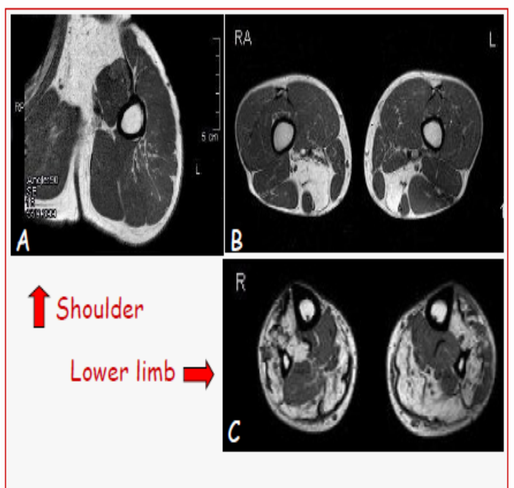
Pts. II-2, II-4, II-5 had over 5-fold increased expression of ***miR-206, miR-133a, miR-133b*** as compared to control. This elevation was not found in one heterozygous carrier (pt. III-1). The levels of ***miR-133b*** (marker of residual muscle mass) and ***miR-206*** (marker of muscle regeneration potentiality), correlated with clinical severity.

Total body CT scan of Pt. II-2



Total body CT scan (A) showed fibro-fatty replacement of biceps brachii muscle (B,C), globous heart (B), fibro-fatty replacement of posterior muscles in the thigh (D), such as semimembranosus and semitendinosus (D) and in the leg (E) such as gastrocnemius, median and lateral in the calf (E). Vastus lateralis is relatively spared.

Total body MRI of Pt. II-5



Total body MRI showed relative preservation of deltoid muscle (A), fibro-fatty replacement of posterior muscles in the thigh (B) such as adductor major and leg (C) such as gastrocnemium medialis and lateralis (C), especially on the left.

Conclusions:

- The expression levels of serum miR-206 and miR-133a resulted higher in Pt.II-5 as compared to Pt.II-2 and II-4 (affected) as well as in the heterozygous carrier Pt. III-1.
- Circulating myo-MiRNA are biomarkers of muscle differentiation (miR-206) and of regeneration potential (miR-133a).
- There is an inverse correlation between atrophy demonstrated by muscle imaging and myo-miRNAs, which can be used as non-invasive biomarkers of disease severity.
- The clinical and molecular aspects on NLSD-M are not fully characterized, but insight from such results are important both to understand mechanism of muscle atrophy and cellular content of triglycerides in muscle fibers.
- In clinical trials the effect of the use of medium-chain-triglyceride to decrease triglyceride storage can be monitored by muscle imaging and myo-miRNA expression.

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