POSTER

PS2Group1-026 / #478

Topic: *Group 1 – Muscle Diseases of Genetic Origin: Clinical Features, Pathophysiology, Therapy / 1.2 Muscle Dystrophies (Non-Dystrophinopathy)*

CALPAINOPATHIES IN CHILE

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Abstract: Limb girdle muscular dystrophy 2A (LG- MD2A; MIM # 253600) is an autosomal recessive disorder caused by mutations of the *CAPN3* gene, which encodes for calpain-3 (CAPN3), a muscle specific calcium-activated neutral protease involved in remodelling of the sarcomere. No patients with calpainopathy have been reported hitherto from Chile. Herein, we describe five patients belonging to four unrelated Chilean families harbouring muta- tions of the *CAPN3* gene. Patient 1 is a 26-year-old female that presented with proximal lower limb weakness since she was 8 years old. She had severe

bilateral Achilles tendon retraction that determined a tiptoe gait. She showed hyperlordosis and scapular winging. CK levels were elevated 45-fold. Patients 2 and 3 are two sisters born from a consanguineous marriage. The older sister (Patient 2) presented gen- eralized weakness since she was 7 years old. She walked in tiptoes and underwent a left Achilles te- notomy due to a severe retraction. She showed se- vere proximal pelvic and shoulder girdles weakness, hyperlordosis and mild scapular winging. CK levels were within normal range. Her younger sister (Pa- tient 3) complained of proximal lower limb weak- ness since she was 25-years old, and showed severe weakness of the pelvic girdle, associated with distal lower limb involvement and bilateral Achilles re- traction. The shoulder girdle was less affected, but presented severe scapular winging. Serum CK levels showed a 5-fold increase. Patient 4 is a 21-year old male that presented delayed motor milestones and increased lower limb weakness since he was 12-years old. He showed a marked amyotrophy of the ischiotibial and adductor muscles on the thighs, with relative sparing of the quadriceps, and a severe impairment in the posterior leg compartments. He shows a scapular winging and anterior arm compart- ment involvement. CK levels were increased by 34-fold. Patient 5 is the only child of a non-consan- guineous marriage, with a history of tiptoe walking associated with calf pain after exercise since he was 10-years old. He presented discrete scapular wing- ing,

diffuse amyotrophy, mild gastrocnemius hyper- trophy and selective distal biceps hypotrophy. Muscle strength showed a predominantly proximal limb girdle weakness, with Achilles and elbow re- tractions. CK levels showed a 63-fold increase. The muscle biopsies of all patients showed a non- specif- ic dystrophic pattern, with eosinophilic infiltrates in patient 5. None of the patients showed cardiac or re- spiratory compromise. Whole body muscle MRI performed to patients 1 to 4 showing a variable de- gree of fatty replacement, according to disease dura- tion, following the pattern described for LGMD2A. Genetic screening for LGMD mutations was per- formed in the four patients on a NGS panel of 306 genes involved in neuromuscular diseases, using HaloPlex (Agilent Technologies^{TM}) enrichment method and sequenced on the NextSeq500 (Illumi- na^{TM}) by Helixio^{TM} (Biopôle Clermont-Limagne, France). The screening allowed the identification of the variant p.Arg788Serfs*14 of the *CAPN3* gene (NM_000070.2) for patients 2 and 3; as well as nov- el mutation p.Gly36Valfs*21 found in a homozy-

gous state for Patient 4 and in a compound heterozygous state, associated with variants p.Arg- 748Gln and p.Arg788Serfs*14 for patient 1 and 5 respectively. FONDECYT Grant 1151383.