GOSR 2: A novel form of Congenital Muscular Dystrophy

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We describe an 36 week male who was born with mild hypotonia and subsequently found to have severe developmental delay. There is also reported optic nerve atrophy. Serum creatine kinase (CK) was 5582. MRI of the brain demonstrated periventricular white matter loss, ventriculomegaly, and a thin corpus callosum. His muscle biopsy demonstrated severe non-specific dystrophic changes. Staining with VLA4-1, however, demonstrated normal levels of glycosylated alpha-dystroglycan, and genetic testing for genes known to cause Walker-Warburg Syndrome (WWS) was negative. Whole exome sequencing was performed, which demonstrated compound heterozygous mutations in GOSR2, including a previously described mutation c.430G > T as well as a novel splice site mutation c.336 + 1G > A.

Previous reports have described homozygous c.430G > T mutations as causative of progressive myoclonus epilepsy (PME), a syndrome characterized by myoclonus, seizures, and progressive cognitive decline. Patients with this GOSR2 mutation also have areflexia, tremors, ataxia, and mildly elevated CK levels, suggesting a possible subclinical myopathy. Muscle biopsies on these PME patients, however, have been normal. Interestingly, at 28 months of age, the patient began to experience clinical seizures with one episode of status epilepticus.

GOSR2 encodes for a SNARE involved with protein transport from the endoplasmic reticulum to the trans-Golgi apparatus. Our studies suggest that GOSR2 may play a role in the transport of critical membrane glycoprotein complexes of myocytes.

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Congenital muscular dystrophy phenotype with excess of neuromuscular spindles in a 5-year old girl

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We report on a 5-year-old girl who presents with an association between a congenital muscular dystrophy, and very peculiar abnormalities on muscle biopsy. The girl was the second child from healthy non related Algerian parents and has now a healthy younger brother. Family history was not informative. Weak fetal movements and polyhydramnios were noticed during the pregnancy. At birth, the child presented with moderate hypotonia, pectus excavatum, mild dysmorphism, club foot, adducted thumbs and generalized proximal arthrogryposis. The girl showed normal intelligence. She had acquired a sitting position, but no ambulation or standing position. She presented with severe shoulder, hip and knee contractures contrasting with distal hyperlaxity. In addition, there was severe kyphosis and a mild scoliosis. Weakness was axial, proximal and distal, facial musculature being mostly spared. A mild right strabismus was noted. The child also presents with mitral valve dysplasia with insufficiency that required surgical correction. There was no need for ventilatory support.

Whole Body Muscular MRI demonstrated a diffuse hypotrophy of muscles without selective pattern of involvement. No abnormalities suggestive of collagen VI-related myopathy or other known myopathies were identified. Immunolabelling of collagen VI in cultured fibroblasts demonstrated the absence of secretion and intracytoplasmic retension, but no mutation was detected in the COL6A1-3 genes. Muscle biopsy especially showed a dense conjunctive tissue harboring numerous ovoid formations corresponding to the neuromuscular spindle. There were only few "extra-fusal" muscle fibres. No necrotic regenerative fibers were observed. To our knowledge, this pathologiacal aspect on the biopsy has only been described in patients with HRAS mutations (test ongoing), but in contrast with the previously reported cases, the child does not present organomegaly or hypertrophic cardiomegaly and is still living at five years of age.

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DYSTROPHINOPATHY: FUNCTIONAL EVALUATION AND ORGAN INVOLVEMENT

P.2.1

The NorthStar Ambulatory Assessment in Duchenne Muscular Dystrophy: Considerations for the design of clinical trials

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With the emergence of experimental therapies for Duchenne Muscular Dystrophy, it is crucial to have precise and current information on the natural history of this disorder to properly design clinical trials. The aims of this study were to observe the motor function decline of ambulant DMD boys treated according to nationally agreed standards of care; and describe this decline in the genetic subpopulations of different skippable deletions (by exon 44, 45, 50, 51, 53). Through the NorthStar Network and database, clinical data systematically collected from 2004 to 2012 on 483 DMD boys followed-up in 17 UK neuromuscular centres was included in the analysis. For the analysis of the genetic subpopulation we included data from 54 DMD boys followed-up in Rome. Our study focuses on the NorthStar Ambulatory Assessment (NSAA) as a primary outcome measure. We reported that boys, who started steroids before 5 years of age, gain better motor function until age 7 (p = 0.04). Including all corticosteroid treatment regimens, we observed that after age 7 when boys start declining, the slope is of approximately 3.5 units in NSAA per year. The median age at loss of ambulation was 13 years, and two years prior to loss of ambulation, the mean total score for the NSAA was 13.5 units. When compared with the whole cohort of DMD boys, individuals skippable by exon 44 and 46 did better, declining at a slower rate (p = 0.004), while populations skippable by exon 53 and 52 showed a faster decline (p = 0.05). Our study provides important information on the current natural history of DMD. The analysis on motor function decline in different patient sub-population is of help when selecting inclusion criteria in the design for clinical trials.

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