## Whole body MRI WB-MRI *MRI in the diagnosis and monitoring neuromuscular diseases*

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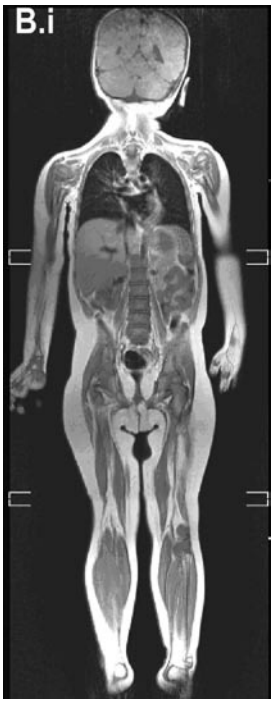


There have been extraordinary advances in the last two decades in the identification of the genetic defects causative of many of hereditary neuromuscular disorders, but diagnosis often remains challenging due to the great clinical and genetic heterogeneity, the lack of specificity of complementary tests and the limited availability and complexity of molecular diagnosis of many of these entities. Muscle imaging has recently become a part of the diagnostic work-up of acquired and inherited muscle diseases. Magnetic resonance imaging (MRI) is the method of choice because it is free of radiation or side-effects, and has excellent soft tissue contrast and resolution. It allows detection of changes resulting from fat infiltration into muscular mass and decrease of muscular volume, with distinction from one muscle to another even within the same functional group. Another interest of muscle MRI is the potential of MRI to provide truly quantitative and objective data to assess change over time without requiring invasive procedures such as biopsy and potentially showing results more rapidly than when assessing functional change. The limited number of sensitive outcome measures in this field and the need to avoid invasive techniques in a patient population where muscle function is already compromised makes MRI particularly attractive in this regard, and this is reflected in an increasing interest in quantitative MRI outcome measures. The intrinsic contrast of muscle tissue with MRI is incomparably richer than with other techniques and can be manipulated

to sensitize signal specifically to many different variables, from fat or fibrosis to perfusion and oxygenation.

Recently, guidelines have been published by an international work group (Kieren et al 2012) Three protocols were priority selected: (I) T1-weighted (T1w) imaging, for the screening of disease extension; (II) Proton-density weighted (PDw) imaging with water–fat separation, for the quantitation of fatty infiltration; and (III) Parametric T2 imaging, for the quantitation of inflammation.

Proton-density weighted (PDw) imaging with water–fat separation is being investigated both preclinically in animal models to assess the course of neuromuscular disease and clinically in natural history studies and drug trials.

The major development of muscle MRI techniques at present is focused in the impact of the technique in diagnosis of muscle disorders. T1-weighted sequences detect both muscle atrophy and increased signal related to adipose tissue, and are therefore the most useful images. Subcutaneous fat distribution is also adequately visualized, which is particularly relevant to entities that can be associated with lipoatrophy (myopathy due to mutations in *LMNA* and *SEPN1* genes). STIR sequences may be interesting if cerebral white matter signal changes and muscle edema and/or inflammation are likely to happen (congenital muscular dystrophy, dysferlinopathy, FSH, inflammatory myopathy). Sequential MRI studies, mainly in lower limbs, have reported distinct patterns of muscle involvement of thighs and legs in various forms of inherited myopathies (*COL6, SEPN1, RYR1, LMNA, DNM2)*. More recently, whole-body MRI (WB-MRI) techniques have been developed and may enhance significantly the diagnostic potential of the sequential scanning techniques in many neuromuscular disorders with more diffuse involvement.

WBMRI allows visualizing in axial and frontal views muscles of the body from head to toes. It offers not only the equivalent of multiple sequential MRI studies for all body regions (head, neck, trunk, girdles, limbs, thorax, abdomen), but also frontal views. This is important because frontal views better explore certain muscles and nerves that follow the longitudinal axis (psoas, SCM, neck and cranial muscles, sciatic nerve), may reveal heterogeneous involvement all along the longitudinal bulk, and allow distinction between closely apposed muscles.

Neuromuscular disorders with onset in childhood are usually inherited, with spinal muscular atrophy (SMA) the congenital myopathies (CM) and the congenital muscular dystrophies (CMD) being the most frequent entities , presenting early in life with generalized hypotonia, weakness and motor delay. Topography of weakness is variable and often diffuse, and patients may develop orthopaedic complications (scoliosis, joint contractures), cardiac, respiratory or bulbar dysfunction. Progressive and later onset muscular dystrophies show mainly a limb-girdle distribution of the muscle weakness (limb-girdle muscular dystrophies or LGMD). Children and in general neuromuscular patients often constitute a challenge for WBMRI studies due mainly to motor, orthopaedic and respiratory symptoms and this requires a specific approach for defining a satisfactory protocol in terms of quality of image and examination time. A preliminary protocol using a 1.5-Tesla MRI system was defined in our clinic in order to analyze feasibility and quality of images. The results have been presented previously in a World Muscle Society Meeting (Cuvelier et al, 2006). Suboptimal or incomplete studies were obtained in young children with short stature and in patients with very retractile phenotypes showing severe hip and knee retractions. Several changes in parameters and technical settings allowed us to

establish a final protocol that we use now in the everyday clinic (Quijano-Roy et al 2012) This protocol with a pediatric and an adult version seems simple and reasonably short to perform (in time around 30-40 minutes). Sedation in young non cooperative children by a protocol using rectal NEMBUTAL® and oral MELATONIN is usually effective. Occasionally, a parent may be scanned simultaneously in the same MR-table to reassure the child during the procedure. Technical setting, tolerance is usually adequate and muscle cartography of the whole body is obtained (brain-head, neck, trunk, limbs, girdles, intercostal ant thoracic region, paravertebral, abdominal muscles), with good quality and informative images, even in young children, individuals with severe joint contractures, mechanically ventilated or carrying metallic implants.

We have recently reviewed the WBMRI examinations in 117 individuals including young children, patients with severe limb contractures, and children receiving ventilatory support or with metallic implants. 38 subjects had a genetically confirmed diagnosis (*RYR1, LMNA, COL6, DNM2, GAA, TPM2, SGCA, MYH7, NEB, SMN*). T1-TSE WBMRI sequences were reviewed and were abnormal in 67 % of the 106 patients, and unexpectedly in 27% of the 11 asymptomatic relatives. Diffuse striped signal abnormalities ('tiger-like') were very specific of ColVI-related myopathy. In addition, distinct involvement of muscles in the head, neck, trunk, girdles and limbs was observed in patients with *RYR1, SEPN1, GAA, LMNA or TPM2* mutations, leading to quite specific recognisable patterns in 34 patients. Abnormalities and pattern recognition were more frequent in patients studied due to selective spinal stiffness or scoliosis (80% abnormal, recognizable in 75% of cases) hyperlaxity syndrome (75%; 50%), or with confirmed myopathy but absence of these particular markers (71%; 40%). Pattern was compatible with the molecular diagnosis in

97%. Mild clinical involvement was revealed by muscle testing in 3 parents with abnormal WBMRI.

Concerning neurogenic disorders WBMRI showed distinct features in two patients with type 3 SMA that were suspected of having a myopathy, in particular a 'ragged' aspect of the tissue signal and the classical hypertrophy of adductor longus muscle. Very asymmetric involvement supported the clinical diagnosis of poliomyelitis in a boy with unclear antecedents. The results of WBMRI in arthrogrypotic syndromes and in the hyperlaxity one, profiles with distinct features but not previously identified helped ruling out reasonably known entities, leading to further research for new gene identification. On the other hand, most patients with an unspecific phenotype of neuromuscular disease or developmental delay without hyper CK had normal MRI. These results do not exclude completely muscle disease but may prone clinicians to explore other diagnostic possibilities, in particular chromosomal or neuro-developmental syndromes if cognition is impaired. In contrast, our study shows that, in patients with significant anomalies on MRI, a muscle or neurogenic disease is likely to occur. Finally, WBMRI was very useful in family studies because it detected or excluded muscle involvement in relatives, with an excellent correlation with the genetic findings.

Overall, WB-MRI seems particularly useful in patients with indeterminate clinical or histological features of neuromuscular disease, especially if lower limb MRI features are not diagnostic. WB-MRI is a useful diagnostic tool when clinical neuromuscular findings suggest a disorder caused by mutations in genes which are difficult to analyse (RYR1, COL6, NEB), when gene variants of unknown pathogenicity are found or in cases where the disease has poor tissue specific markers (LMNA, SEPN1, GAA, SMN). Although

additional observations in specific genetic entities are necessary and will improve confidence in use of WB-MRI to differentiate between different neuromuscular disorders, it is already a valuable element in the diagnosis and monitoring of neuromuscular disorders in children. It has the potential to provide valuable assistance in interpretation of complex data from new molecular techniques such as whole-genome or exome sequencing and SNP-CGH array.