Investigating GSD type III patients with multi-parametric functional NMR imaging and spectroscopy

C. Wary¹, C. Baligand¹, A. Nadaj-Pakleza², A. Monnet¹, P. Labrune⁴, B. Eymard¹, P. Laforêt¹, and P. G. Carlier¹

¹NMR Laboratory AIM CEA, Institute of Myology, Paris, France, ²Institute of Myology, Paris, France, ³Department of Neurology, Medical University of Warsaw, Warsaw, Poland, ⁴Department of pediatrics, Antoine Béclère Hospital, Clamart, France

INTRODUCTION
Debranching enzyme deficiency, or glycogen storage disorder III (GSD 3) is a rare autosomal recessive disorder, with over 50 identified mutations on the single AGL gene of chromosome 1p21, and has a clinically heterogeneous and "morphing" presentation. Often characterized by liver dysfunction in early childhood, with spontaneous remission at puberty, it then frequently evolves to a slowly progressive myopathy of distal muscles in adult life. Dietary therapy has proved efficient for children presenting liver cases of GSD3, but its effect on later muscle involvement is far from established. The mechanisms of the disease, and in particular of the transition from hepatic to muscular involvement are totally unknown. The present NMR study is included in a wider study aiming at improving characterization, understanding, and ultimately therapeutic approaches of GSD3.

MATERIALS AND METHODS
Patients In all, 11 biochemically confirmed GSD 3 patients, (6F, 5M), aged 12 to 67 underwent NMR examinations. Of these 8 have been included in a prospective protocol (patients d-k) and have undergone as complete explorations.

NMRI Laboratory AIM CEA, Institute of Myology, Paris, France, ²Institute of Myology, Paris, France, ³Department of Neurology, Medical University of Warsaw, Warsaw, Poland, ⁴Department of pediatrics, Antoine Béclère Hospital, Clamart, France

RESULTS
Images demonstrated fatty infiltrations and muscle remodeling in all 10 patients. Muscles were altered in the following decreasing order: soleus, vastus medialis, then lateralis of gastrocnemius, peroneus and tibialis anterior. We graded each muscle between 0 for no visible alteration, to 3.

DISCUSSION AND CONCLUSION
As expected for this glycogen storage disorder, and documented on isolated patients, absence of acidosis at exercise [5] and glycogen excess [3, 4] were observed by NMRS, though quantification of glycogen showed a reduction with disease progression. Muscle wasting was also characterized by NMRI, and quantified image analysis could yet improve this index. More unpredictably, the combination of various NMR modalities identified yet unknown abnormalities, such as accumulation of metabolites –possibly glycolytic intermediates– in the PME region at rest (but did not significantly increase at exercise as in GSD VII [6]); impaired oxidative phosphorylation and muscle perfusion which might contribute to symptoms of exercise intolerance. The relation between retarded perfusion responses and altered mitochondrial energetics deserves further investigation. The intrinsic potential of NMR for multi-parametric functional, biochemical and anatomical investigations is rarely exploited. We show here the wealth of information which NMR offers when suitably tailored to address the question of metabolic dysfunction in muscle. It provides several quantitative indices which improve characterization of this rare disorder, might help evaluating the natural progression of GSD3, and potentially future therapy.