

POSTER PRESENTATION

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Characterisation of a novel cardiac phenotype in patients with GFPT1 or DPAGT1 mutations

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From 17th Annual SCMR Scientific Sessions
New Orleans, LA, USA. 16-19 January 2014

Background

Mutations in the GFPT1 and DPAGT1 genes, which encode enzymes associated with roles in protein N-linked glycosylation, have been recently identified in a rare subgroup of patients with congenital myasthenic syndromes (CMSs). These mutations are inherited in an autosomal recessive pattern, and the mechanism of impaired neuromuscular transmission may be acetylcholine receptor (AChR) deficiency due to impaired (AChR) subunit glycosylation. Aberrant protein glycosylation is also implicated in the development of severe cardiomyopathies in the congenital disorders of glycosylation, although the mechanisms responsible for cardiac involvement are unknown. We investigated whether patients with CMS and GFPT1 or DPAGT1 mutations also had evidence of a cardiac phenotype.

Methods

We performed comprehensive cardiovascular magnetic resonance (CMR) imaging at 1.5T (Avanto, Siemens), 31P spectroscopy at 3T (Tim Trio, Siemens) and echocardiography to evaluate cardiac structure and function in patients with GFPT1 (n = 2) and DPAGT1 (n = 2) mutations. The mean age of the participants was 45 (range 25-57) and two were male.

Results

Electrocardiography was abnormal in all, with abnormal repolarisation and deep S waves (n = 3) or marked left ventricular hypertrophy by voltage criteria (n = 1). Despite normal biventricular volumes and systolic function, GFPT1/DPAGT1 patients demonstrated late gadolinium enhancement suggestive of myocardial fibrosis (n = 4, mean proportion of enhanced myocardium > 5 SD

above individual reference regions 3.2% +/-1.6, Figure 1), impaired energetics (n = 2) and diastolic dysfunction (n = 3). No patient had symptoms attributable to cardiovascular disease on structured interview.

Conclusions

Patients with GFPT1 or DPAGT1 mutations demonstrate a cardiac phenotype including abnormal electrocardiography, myocardial fibrosis, diastolic dysfunction and impaired energetics, despite normal systolic function. These findings may reflect incipient cardiomyopathy due to aberrant cardiac glycoprotein function. The reason for

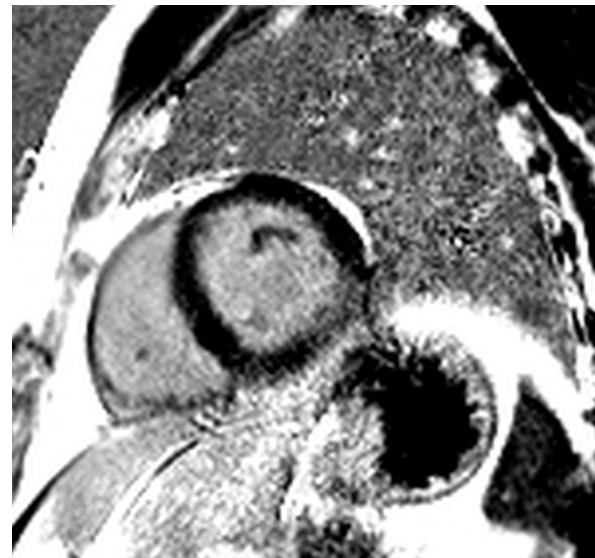


Figure 1 Representative electrocardiograph demonstrating repolarization abnormalities with inversion of T-waves in inferolateral leads and deep S waves.

Table 1

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Reference range |
|------------------------------------------|---------------------------------------------|----------------------------|---------------------------|---------------------------------|--------------------------------------|
| Age/years | 57 | 58 | 38 | 25 | |
| Gender | Female | Female | Male | Male | |
| Mutation | DPAGT1 | DPAGT1 | GFPT1 | GFPT1 | |
| Nucleotide change | c.349G > A c.699dup | c.478G > A c.574G > A | c.44C > T c.1486C > T | c.1154G > A c.1301G > A | |
| Effect on protein | p.Val117Ile p.Thr234Hisfs*116 | p.Gly160Ser p.Gly192Ser | p.Thr15Met p.Arg496Trp | p.Arg385His p.Arg434His | |
| LVEDV/ml | 104 | 142 | 124 | 144 | 102-218 ml (male) 83-187 (female) |
| LVESV/ml | 29 | 53 | 41 | 46 | 18-82 ml (male) 18-66 ml (female) |
| LVEF | 72 | 63 | 67 | 68 | 57-81% (male and female) |
| RVEF | 75 | 64 | 66 | 70 | 47-71% (male) 53-73% (female) |
| LV mass/g | 120 | 115 | 134 | 124 | 81-165 g (male) 42-150 g (female) |
| LGE regions | Anterior septum and inferior LV/RV junction | Basal inferolateral wall | Basal inferolateral wall | Inferior and inferolateral wall | |
| LGE > 5SD/% | 1.6 | 2.3 | 5.1 | 3.9 | |
| Stress perfusion CMR (visual assessment) | Normal | Not performed | Normal | Normal | |
| PCr/ATP ratio | 1.19 | 1.01 | 2.23 | 2.25 | |
| Diastolic function | Grade 1 dysfunction | Grade 2 dysfunction | Grade 1 dysfunction | Normal | |

Baseline characteristics and CMR and echo indices including left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), left ventricular ejection fraction (LVEF), right ventricular ejection fraction (RVEF), late gadolinium enhancement (LGE) and phosphocreatine to adenosine triphosphate ratio (PCr/ATP).

the milder phenotype than is seen many congenital disorders of glycosylation may be greater residual enzyme function as a consequence of a less pathogenic mutation. This study highlights the utility of CMR for the assessment of rare cardiac phenotypes and reinforces the need for cardiac surveillance in patients with undefined or uncharacterised neuromuscular disorders due to glycosylation pathway defects.

Funding

British Heart Foundation.

Published: 16 January 2014

doi:10.1186/1532-429X-16-S1-P332

Cite this article as: Lewis *et al.*: Characterisation of a novel cardiac phenotype in patients with GFPT1 or DPAGT1 mutations. *Journal of Cardiovascular Magnetic Resonance* 2014 **16**(Suppl 1):P332.

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