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Respiratory and cardiac function in congenital muscular dystrophies with alpha dystroglycan deficiency

M. Pane [a], S. Messina [a,b], G. Vasco [a], A.R. Foley [c], L. Morandi [d], E. Pegoraro [e], T. Mongini [f], A. D'Amico [g], F. Bianco [a], M.E. Lombardo [a], R. Scalise [a], C. Bruno [h], A. Berardinelli [i], A. Pini [l], I. Moroni [d], M. Mora [d], A. Toscano [b], M. Moggio [m], G. Comi [m], F.M. Santorelli [g], E. Bertini [g], F. Muntoni [c], E. Mercuri [a,c,*]

[a] *Department of Paediatric Neurology, Catholic University, Rome, Italy*
[b] *Department of Neurosciences, Psychiatry and Anaesthesiology, University of Messina, Italy*
[c] *Dubowitz Neuromuscular Centre, University College London Institute of Child Health and Great Ormond Street Hospital for Children, London, United Kingdom*
[d] *Myopathology and Neuroimmunolgy, Pediatric Neurology and Neuroradiology Units, Neurological Institute C. Besta, Milan, Italy*
[e] *Department of Neurosciences and Psychiatry and Anaesthesiology, University of Padova, Italy*
[f] *Neuromuscular Center, S.G. Battista Hospital, University of Turin, Italy*
[g] *Department of Laboratory Medicine, Unit of Molecular Medicine, Bambino Gesù Hospital, Rome, Italy*
[h] *Neuromuscular Disease Unit, G. Gaslini Institute, Genoa, Italy*
[i] *IRCCS "C. Mondino" Foundation, University of Pavia, Italy*
[l] *Child Neurology and Psychiatry Unit, Maggiore Hospital, Bologna, Italy*
[m] *Dino Ferrari Center, Department of Neurological Science, University of Milan, Italy*

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Abstract

The aim of this retrospective study was to assess respiratory and cardiac function in a large cohort of patients with congenital muscular dystrophies (CMD) with reduced glycosylation of alphadystroglycan (α-DG). Thirteen of the 115 patients included in the study died between the age of 1 month and 20 years. The age at last follow up of the surviving 102 ranged between 1 year and 68 years (median: 9.3 years). Cardiac involvement was found in 7 of the 115 (6%), 5 with dilated cardiomyopathy, 1 cardiac conductions defects and 1 mitral regurgitation. Respiratory function was impaired in 14 (12%). Ten of the 14 required non invasive nocturnal respiratory support, while the other four required invasive ventilation. Cardiac or respiratory involvement was found in patients with mutations in *FKRP*, *POMT1*, *POMT2*. All of the patients in whom mutation in POMGnT1 were identified had normal cardiac and respiratory function. Published by Elsevier B.V.

Keywords: Congenital muscular dystrophy; Alpha dystroglycan; Heart; Respiratory

1. Introduction

The term "dystroglycanopathies" has been used to describe a genetically heterogeneous group of muscle disorders with a muscle biopsy showing dystrophic features and a reduction of α-dystroglycan (α-DG) with frequently associated central nervous system involvement [1].

The spectrum of clinical phenotypes ranges from the severe Walker–Warburg syndrome (WWS), muscle–eye–brain disease (MEB) and Fukuyama congenital muscular dystrophy (FCMD), all with severe muscle, eye and brain involvement, to mild cases of limb girdle muscular dystrophies with late onset and no brain or eye involvement.

* Corresponding author. Address: Department of Paediatric Neurology, Catholic University, Rome, Italy.
E-mail address: mercuri@rm.unicatt.it (E. Mercuri).

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Until recently a dystroglycanopathy phenotype has been found associated with mutations in six genes coding for putative and demonstrated glycosyltransferases or accessory proteins of glycosyltransferases : *Protein-O-mannosyl transferase 1* (*POMT1*; OMIM 607423), *Protein-O-mannosyl transferase 2* (*POMT2*; OMIM 607439), *Protein-O-mannose 1,2-N-acetylglucosaminyltransferase 1* (*POMGnT1*; OMIM 606822), *fukutin* (*FKTN*; OMIM 607440), *Fukutin-related protein* (*FKRP*; OMIM 606596) and *LARGE* (OMIM 603590) [2–7]. Recent suggestions that congenital muscular dystrophy (CMD) secondary to decreased α-dystroglycan expression may also be found associated with N-glycosylation disorders or mutations in dystroglycan itself are still limited to single cases [8].

Patients with dystroglycanopathies have common features, such as predominant involvement of the upper limbs and elevated CK but the spectrum of clinical severity ranges from the severe WWS, MEB and FCMD with severe structural muscle, eye and brain involvement, to milder cases with late onset and no brain or eye involvement.

Two studies on large cohorts have demonstrated that mutations in individual genes can be associated with different phenotypes and that, conversely, the same phenotype can be found in association with different known genes. [9,10]. Approximately half of the dystroglycanopathy patients do not have mutations in the known genes, this suggesting further genetic heterogeneity [9,10]. Patients with unknown mutations often have similar phenotypes to the cases in whom mutations have been identified, these findings strongly suggesting that the identity of the defective gene (or the absence of mutations in the known genes) cannot be predicted from the clinical phenotype.

All the previous studies reporting phenotypes in patients with known and unknown mutations have mainly focused on brain and eye involvement and maximal functional ability while little has been reported about other clinical aspects, such as severity of cardiac or respiratory involvement, which are common in other forms of congenital muscular dystrophy [11,12].

The aim of this retrospective study was to review respiratory and cardiac data in a large cohort of patients with CMD and reduction of alpha dystroglycan and their relationship with genetic and brain MRI findings.

2. Patients and methods

2.1. Patients

All patients had a diagnosis of CMD with α-DG deficiency. Inclusion criteria were early presentation (neonatal or delayed acquisition early milestones), myopathic/dystrophic changes on muscle biopsy, and deficiency of α-DG on the sarcolemma of skeletal muscle fibers [13,14].

Because of the possible overlap with early onset limb girdle muscular dystrophies, it has recently been suggested that CMD should include cases with onset of weakness prenatally or within the first months of life, before ambulation is acquired. LGMD in contrast, would include the cases with onset after ambulation has been acquired.

All the patients included in this study had already been included in two previous large multicentric studies reporting muscle, eye and brain involvement and motor abilities. Details of the cohorts and of their genetic background, including methodology in genetic screening have already been reported [9,10]. We limited this study to those patients who had been seen at least once at one of the participating centers and in whom there was at least one assessment of cardiac and respiratory function.

2.2. Clinical data

Data were collected retrospectively using a structured proforma, noting information from overnight oximetry sleep studies and, when available, forced vital capacity (FVC) and cardiac function studies including electrocardiography (ECG) and echocardiogram results.

Echocardiogram was defined as abnormal if there were congenital abnormalities, signs of dilated cardiomyopathy or of decreased left ventricular systolic function.

3. Results

One hundred and fifteen patients fulfilled the inclusion criteria. Thirteen of the 115 died between 1 month and 20 years. The age at last follow up of the surviving 102 ranged between 1 year and 68 years (median: 9.3 years).

All data were analyzed subdividing the respiratory and cardiac function according to genetic findings and to the classification of phenotypes based on MRI and cognitive findings [9,10].

3.1. Cardiac function

Only 7 of the 115 had signs of cardiac involvement, 5 had dilated cardiomyopathy, one had mitral valve regurgitation and one mild conduction defects. There was no specific association between mutations or clinical phenotypes and cardiac function (Tables 1–3). On echocardiography another child was found to have aortic coartation but no ECG or echocardiogram abnormality.

3.2. Respiratory function

All patients had at least one measurement of overnight oxygen saturation. Fourteen of the 115 (12%) required ventilator support at the time of this study. Ten of these 14 patients had signs of nocturnal hypoventilation and were started on non invasive respiratory support, while the other four required tracheostomy due to acute respiratory distress. Table 1 shows details of the patients with respiratory impairment. There was no specific correlation between mutations or clinical phenotypes and respiratory function (Tables 2 and 3).

Table 1
Individual details of patients with abnormal cardiac or respiratory findings.

Patient	Mutation	Brain MRI	Non invasive ventilation/age	Tracheostomy/age	Cardiac involvement	Age at onset	Age follow up	Age at death
1	FKRP	Normal	–	–	DCM	4 years	–	6 years
2	FKRP	MEB	–	–	DCM	2 years	4 years	–
3	FKRP	Normal	–	–	DCM	4 years	7 years	–
4	POMT1	Normal	–	–	DCM	19 years	20 years	–
5	POMT2	MEB	–	–	DCM			–
6	Negative	Atrophy	–	–	Conductions defects	58 years	68 years	–
7	Negative	Normal	–	–	Mitral regurgitation	12 years	14 years	–
8	Negative	Normal	Neonatal	–	–	–	5 years	–
9	Negative	MEB	Neonatal	–	–	–	–	1 month
10	Negative	Atrophy	Neonatal	–	–	–	10 years	–
11	Negative	Normal	Neonatal	–	–	–	9 years	–
12	FKRP	White matter	6 months	–	–	–	8 years	–
13	FKRP	Normal	9 years	–	–	–	10 years	–
14	FKRP	Normal	13 years	–	–	–	14 years	–
15	POMT2	Hydrocephalus	19 years	–	–	–	–	20 years
16	Negative	White matter	20 years	–	–	–	21 years	
17	Negative	Cerebellar	–	Neonatal	–	–	6 years	
18	POMT2	Cerebellar	–	3 years	–	–	13 years	
19	Negative	Cerebellar	–	4 years	–	–	–	6 years
20	Negative	Cerebellar	–	–	–	–	–	7 months
21	Negative	Cerebellar	–	–	–	–	–	16 months
22	Negative	Cerebellar	–	–	–	–	–	13 years
23	POMT2	Cerebellar	–	7 years	–	–	–	12 years
24	POMGnT1	MEB						neonatal
25	POMT1	WWS	–	–	–	–	–	4 years
26	POMT2	WWS						Neonatal
27	Negative	WWS						Neonatal
28	Negative	WWS						Neonatal

MEB, muscle eye brain disease; WWS, Walker Warburg syndrome; DCM, dilated cardiomyopathy.

Table 2
Genetic and clinical findings.

	Abnormal cardiac function	Respiratory failure	Death
FKRP ($n = 13$)	3/13 (23%)	3/13 (23%)	1/13 (7.6%)
POMT1 ($n = 14$)	1/14 (7 %)	1/14 (7%)	1/14 (7%)
POMT2 ($n = 10$)	1/10 (1%)	3/10 (3%)	3/10 (3%)
POMGNT1 ($n = 18$)	0/18	0/18	1/18 (5.5%)
LARGE ($n = 2$)	0/2	0/2	0/2
FKTN ($n = 1$)	0/1	0/1	0/1
All negative ($n = 57$)	2/57 (3.5%)	7/57 (12%)	7/57(12%)

Table 3
Brain MRI and clinical findings.

	Abnormal cardiac function	Respiratory failure	Death
Normal brain MRI, no mental retardation ($n = 8$)	3/8 (37.5%)	2/8 (25%)	1/8 (12.5%)
Normal brain MRI, mental retardation ($n = 26$)	1/26 (3.8%)	3/26 (11.5%)	0/26
Cerebellar involvement ($n = 20$)	0/20	4/20 (20%)	5/20 (25%)
MEB ($n = 35$)	2/35 (5.7%)	1/35 (2.8%)	2/35 (5.7%)
WWS ($n = 8$)	0/8	0/8	4/8 (50%)
Hydrocephalus/Chiari ($n = 7$)	0/7	1/7 (14%)	1/7 (14%)
Brain atrophy ($n = 5$)	1/5 (20%)	1/5 (20%)	0/5
White matter ($n = 6$)	0/6	2/6 (33%)	0/6

FVC could not be reliably recorded in the majority of the patients due to young age, lack of collaboration secondary to mental retardation, or macroglossia or malocclusion.

3.3. Survival

Thirteen patients died, four from intractable seizures and the other nine for severe acute events leading to respiratory failure (Tables 1–3). No postmortem was performed to ascertain causes of death.

4. Discussion

The aim of this retrospective study was to assess cardiac and respiratory function in a large cohort of patients with CMD and reduction of α-dystroglycan on muscle biopsy. Cardiac function was found to be impaired in only 7 of the 115 children. These patients carried mutations in *FKRP*, *POMT1* and *POMT2*. One patient with *LARGE* mutations had an aortic coartation but no signs of primary cardiac involvement.

Cardiac abnormalities have already been reported in CMD patients with dystroglycanopathies [15–18], mainly associated with FKRP and fukutin mutations. In particular, dilated cardiomyopathy has been found to occur frequently in patients with FKRP mutations and LGMD2I phenotype [19–22] but has also been reported in five cases of patients with CMD phenotype [15,23–25]. In our cohort including only CMD patients, cardiac involvement was found in 3 of the 13 patients with FKRP mutations, two of whom had already been reported [15].

We also found dilated cardiomyopathy in a patient carrying POMT2 mutation and in one patient with POMT1 mutations. To our knowledge, with the exception of a report of left ventricular hypertrophy in a patient with POMT2 mutations [18], this is the first report of cardiac involvement in patients with CMD due to POMT1 and POMT2 mutations.

As we only had one patient with *FKTN* mutations and two with *LARGE* mutations we cannot draw any conclusion on possible cardiac involvement that has been previously reported to be frequent in patients with CMD and *FKTN* mutations in Japan [17].

Cardiac involvement appeared to occur infrequently in the groups without mutations in the known genes. Only one patient developed conduction defects at the age of 58 years.

Our findings confirm previous observations that cardiac impairment is relatively rare in this group of disorders. When found, cardiac abnormalities were already present before 12 years of age in 4 of the 7 cases. We believe that the low detection rate cannot be attributed to the age of the patients studied as more than 35% of our cohort was above the age of 12 and, in 5 cases, above the age of 20 years at the time of the study.

Impairment of respiratory function was also not common, occurring in only 14 of the 115 (12%) patients. Unfortunately, because of age, limited cooperation, mental retardation and in a number of cases, macroglossia or malocclusion, the majority of patients did not have reliable measurements of FVC and we cannot provide an estimate of their values according to age. Sleep studies however were available in all patients studied, with 14 patients requiring ventilator support. Four of the 14 required invasive ventilation, inserted following an acute episode of respiratory distress. The other 10 had abnormal sleep studies which prompted the initiation of non invasive nocturnal ventilation. In 6 of the 10 ventilation was required before the age of one year.

Overall respiratory problems were also not frequent and not specifically associated with any of the known dystroglycanopathy genes or individual phenotypes even though they were relatively more common in the patients with *FKRP* mutations, with normal brain MRI findings and no mental retardation, in those with *POMT1 and POMT2* mutations with cerebellar involvement, microcephaly and mental retardation, and in a recently reported subgroup of CMD patients with severe intractable epilepsy [25]. The group with intractable epilepsy was also at higher risk of reduced survival as 4 of the 13 patients who died belonged to this subgroup.

In the large group of patients with *POMGnT1* mutations respiratory and cardiac impairment, never occurred even though one patient with MEB phenotype and *POMGnT1* mutations died in the first year for acute events.

Unlike other aspects of phenotype that are related to the severity of the mutations in the dystroglycanopathies, respiratory and cardiac function abnormalities were not specifically associated with the more severe MEB or WWS phenotypes, typically associated with mutations leading to severe functional defects (e.g., involvement of residues crucial for the enzymatic activity or those leading to frameshift and prematurely truncated protein) resulting in the severe brain, eye and muscle involvement. While these patients appear to be at higher risk of acute fatal events, those who survive early childhood do not demonstrate evidence of chronic progressive cardiac or respiratory impairment. In our cohort 4 of the 8 patients with WWS and 2 of the 35 with MEB died within the first years of life but none of the surviving patients with WWS phenotype and only 2 of the 33 surviving MEB patients had cardiac abnormalities or progressive respiratory failure. These data are in agreement with previous limited studies also reporting that cardiac abnormalities are not frequent in WWS or MEB patients [12,26–28]. Since none of the patients who died in our series had autopsy studies, the causes of death were not always entirely clear and for this reason they were described separately. In two patients who died from acute cardiorespiratory complications, assessments performed months preceding death had been reported as normal this suggesting that death may occur due to severe acute cardiorespiratory events in fragile patients who often also have bulbar weakness.

One of the advantages of this study is that includes the largest cohort of CMD patients with dystroglycanopathy reported so far in the literature. The study was only possible because two large networks provided their retrospective data but this has limited the possibility to obtain more

detailed information on cardiac and respiratory function. Although the information collected are enough to exclude that severe signs of cardiac and respiratory impairment are common features in this cohort, prospective longitudinal studies are still needed to obtain more detailed information on the onset and the possible changes of cardiac and respiratory function over time. As many of the patients reported in this study were in the pediatric age, a longer follow up will also help to establish if some of them will develop cardiac and respiratory problems at a later age.

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