Illness-associated muscle weakness in dystroglycanopathies

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ABSTRACT

Objective: To describe the phenomenon of acute illness-associated weakness (AIAW) in patients with dystroglycanopathy (DG), determine the frequency of this phenomenon in DGs, and compare it to the frequency in Duchenne-Becker muscular dystrophy (DBMD).

Methods: Patients enrolled in a DG natural history study provided medical history, including major illnesses or hospitalizations, at enrollment and annually. We noted a recurring syndrome of profound transient weakness in the setting of febrile illness. To determine the frequency of this phenomenon in the DG cohort and compare it to a cohort with another membrane-related muscular dystrophy, DBMD, we surveyed patients (e-survey tool), collecting demographics and information about episodes of sudden progression of weakness and events surrounding the episodes.

Results: Surveys were completed by 52 (56.6%) patients with DG and 51 (27.3%) patients with DBMD. AIAW was reported in 12 (23%) patients with DG and 2 (4%) patients with DBMD (odds ratio 7.35; 95% confidence interval 1.55, 34.77; $p = 0.005$). Altogether (history or survey), 21 patients with DG, with mutations in *FKRP*, *FKTN*, *POMT1*, *POMT2*, or *POMGNT1*, reported AIAW. These events typically occurred in children <7 years old, and the preceding illness usually included respiratory symptoms. In 10 (47.6%) patients with DG, AIAW preceded the diagnosis of muscular dystrophy.

Conclusions: People with DG, across genotypes, can experience acute, transient weakness associated with a febrile illness, a phenomenon that rarely occurs in DBMD. The physiologic basis of this phenomenon is unknown.

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GLOSSARY

AIAW = acute illness-associated weakness; **CI** = confidence interval; **CK** = creatine kinase; **DBMD** = Duchenne-Becker muscular dystrophy; **DG** = dystroglycanopathy; **FCMD** = Fukuyama congenital muscular dystrophy; **IQR** = interquartile range; **LCMV** = lymphocytic choriomeningitis virus; **OR** = odds ratio; **RSV** = respiratory syncytial virus.

Dystroglycanopathies (DGs) comprise a group of autosomal recessive muscular dystrophies caused by hypoglycosylation of α -DG,¹ a major component of the dystrophin glycoprotein complex.¹⁻³ Disruption of this complex leads to decreased membrane stability.¹⁻³ There are 18 known genes that are required for proper α -DG glycosylation, and mutations in any of these results in disease.³

A phenomenon of acute illness-associated weakness (AIAW) has been described in patients with Fukuyama congenital muscular dystrophy (FCMD),⁴⁻⁸ a DG caused by mutations in *FKTN*. Case reports have described this clinical phenomenon in patients with *FKRP* variants,⁹⁻¹² but there are no reported series. The goal of this article is to describe the phenomenon of AIAW in a cohort of patients with DG, including the clinical characteristics and genotypes involved. We compared the frequency of this phenomenon in the DGs with the frequency in another muscle membrane-related muscular dystrophy, Duchenne-Becker muscular dystrophy (DBMD), to determine whether this is common to the membrane-related dystrophies or unique to the DGs.

Supplemental data
at Neurology.org

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METHODS **Standard protocol approvals, registrations, and patient consents.** Institutional review board approval was obtained for all recruitment and data collection for the natural history study and survey. Written informed consent was obtained from all participants or their legal guardians. Consent was obtained for review of medical records. Authorization was obtained for disclosure from patients whose recognizable pictures and videos are included. The DG natural history study is listed on clinicaltrials.gov (NCT00313677).

DG natural history study. Participants were enrolled in the DG natural history study if they had DG as determined by at least one of the following: muscle biopsy showing deficiency of glycosylated α -DG and dystrophic muscle, documented mutations in a known gene, or demonstration of abnormal α -dystroglycan glycosylation in cultured fibroblasts.¹³ The study is ongoing and enrollment criteria have changed over time. From 2006 to 2009, only patients with *FKRP* variants were included; patients could participate remotely by completing surveys, thus a few patients have not participated in full history and examination. Since 2009, all DG phenotypes have been included, and history and examination were required.

At enrollment, patients provided information about medical histories, updated annually. Major illnesses, hospitalizations, and history of disease progression were recorded. If a patient reported AIAW, clinical data were abstracted from patient report and medical record, including any available records from the time of AIAW.

AIAW survey. We developed a survey to determine the frequency of AIAW in patients with DG and patients with DBMD. We invited all patients in the DG natural history study, including those who only participated through completion of surveys, and all patients with DBMD who were actively followed by the University of Iowa neuromuscular clinic to complete the survey. Surveys were mailed to eligible participants in 2011 and in 2016 (to those who were not contacted in 2011) and were offered at clinical or research visits. Age at time of survey was collected on all potential patients. The survey asked about any episodes of sudden weakness, defined as worsening weakness occurring over 1–2 days (see survey tool at Neurology.org), and any event associated with the acute weakness, providing a list of possibilities (surgery, illness or fever, stress, and other with the option to elaborate). Those

who reported acute weakness associated with an illness were asked questions about the episode including number of events, specific motor skills lost, duration of illness, and associated symptoms. Adult participants were encouraged to consult with parents or others about childhood events. We reviewed medical records surrounding the report of AIAW when possible. Patients were contacted by phone if responses on the survey required clarification.

Definition of AIAW. For the purpose of this analysis, we defined the phenomenon of AIAW as weakness that occurred within 1 week of contracting a febrile illness, consistent with what has been reported previously in FCMD.⁵ Those who reported acute weakness after exertion or surgery or if they reported feeling generally weak with every illness they experienced were not included.

Statistical analysis. Age when the survey was conducted was compared between those who completed the survey and those who did not respond to the survey using Wilcoxon rank-sum test. The distribution of genotypes in the DG cohort was compared between those with AIAW and those who did not report AIAW using the Pearson χ^2 test. The proportion with AIAW reported in the survey was compared between DG and DBMD using the Pearson χ^2 test. The odds ratio (OR) (95% confidence interval [CI]) of AIAW for DG relative to DBMD was also calculated. In addition, an age-adjusted OR of AIAW was computed using logistic regression analysis with age at survey as covariate to account for the possible effect of age on AIAW. All statistical analyses were performed using SAS (version 9.2) (SAS Institute, Cary, NC).

RESULTS **AIAW in patients with DG.** Between survey and natural history study, 94 patients were eligible for participation (figure 1). Surveys were sent to 92 patients with DG, and 52 (56.6%) completed surveys. Those who completed the survey were predominantly male (58%), with median age of 18 years (interquartile range [IQR] 12–38 years). Those who did not return the survey were similarly male (64%; $p = 0.536$) but significantly younger (median age 12 years; IQR 6–28 years) ($p = 0.023$).

Of the 52 who completed the survey, 30 patients (58%) reported experiencing sudden weakness; however,

Figure 1 Summary of participation by patients with dystroglycanopathy

AIAW = acute illness-associated weakness.

only 12 of the responses (23% of those who completed the survey) met our criteria for AIAW. The remaining 18 did not meet the criteria of AIAW because they reported weakness following stressful events (n = 4), with lack of sleep (1), after exertion (1), with pregnancy (1), every time they got sick (4), following surgery (2), weakness greater than 7 days after becoming ill (3), fatigue without weakness (1), and weakness not associated with any precipitating factor (1).

Eighty-nine patients had medical history reviewed as part of the DG natural history study. Of these, 15 (17%) reported acute weakness within 7 days following a febrile illness. Together (through medical history, survey, or both), we identified 21 unique patients with DG who reported an episode of AIAW, 12 female and 9 male, from 18 families (2 twin brothers, 2 twin sisters, 1 brother and sister). The table shows clinical features for these patients, and figure 2

Table Patients with dystroglycanopathy with acute illness-associated weakness (AIAW)

Patient	Age at AIAW, y	Sex	Gene	Variants	Admitted to hospital	CK level	Illness symptoms; complications	Treatment during episode	AIAW before MD known ^a	Multiple episodes of weakness
1	0.25	F	<i>FKRP</i>	c.826C>A; c.469 G>C	N		Respiratory and feeding difficulties	Steroids	Y	Y
2	0.75	M	<i>FKRP</i>	c.826C>A; c.918_929delCTACCTCTACGA	N	18,000	Sore throat		Y	N
3	0.83	F	<i>FKRP</i>	Homozygous c.1100T>C	Y	10,646	URTI	Antibiotics	Y	N
4	1	F	<i>POMT1</i>	c.818C>T; c.132A>C	Y		pneumonia; possibly aspiration, hypoxia		N	N
5	1.083	M	<i>FKRP</i>	c.826C>A; 1050_1027delinsTCAA	N	Too high to measure			Y	Y
6	1.083	M	<i>FKRP</i>	c.826C>A; 1050_1027delinsTCAA	N	Too high to measure			Y	Y
7	1.5	M	<i>POMGNT1</i>	c.1769 G>A; c.636C>T	Y		URTI (RSV and likely coxsackievirus)	Antibiotics	N	Y
8	2	M	<i>FKRP</i>	c.826C>A; c.707T>C	N	31,600	"Presumed viral illness"		Y	N
9	2	F	<i>FKRP</i>	c.826C>A; c.1016 G>A	Y	30,000	Sore throat		Y	Y
10	2	F	<i>FKRP</i>	c.826C>A; c.1016 G>A	Y	30,000	Sore throat		Y	Y
11	2	F	<i>FKRP</i>	c.826C>A; c.266C>T	Y	4,700	Fever to 105° with no localizing signs		N	N
12	3	M	<i>FKRP</i>	Homozygous c.826C>A	Y		Febrile seizure		N	N
13	4	M	<i>FKTN</i>	c.647+2084G>T; retrotransposon insertion	Y	600	Sore throat	IV fluids	N	N
14	4	M	<i>FKTN</i>	c.920 G>A; c.1167dupA	N		"Viral illness"	Steroids	N	N
15	4	F	<i>FKTN</i>	c.920 G>A; c.1167dupA	N			Already on steroids	N	N
16	6	F	<i>POMT2</i>	c.1997A>G; c.1116+1 G>A	Y		Influenza (+H1N1); respiratory failure requiring intubation for 2.5 weeks, unable to eat orally requiring G-tube	Antibiotics	Y	Y
17	7	F	<i>POMT2</i>	c.1997A>G; c.1769A>G	N		Bronchitis and strep throat (+ rapid strep)	Steroids and antibiotics ×2	N	N
18	8	F	<i>FKRP</i>	c.826C>A; c.-34C>T	N		Pneumonia	Antibiotics and steroid inhaler	N	N
19	19	M	<i>FKRP</i>	Homozygous c.826C>A	Y		Pneumonia; respiratory distress	Antibiotics and already on steroids	N	N
20	27	F	<i>FKRP</i>	Homozygous c.826C>A	Y	11,000	Herpangina (coxsackievirus); viral meningitis		Y	N
21	38	F	<i>FKRP</i>	Homozygous c.826C>A	N		Diarrhea and lightheaded		N	N

Abbreviations: CK = creatine kinase; MD = muscular dystrophy; RSV = respiratory syncytial virus; URTI = upper respiratory infection.

^aPatients were thought to be healthy prior to the episode of AIAW, and they were diagnosed with MD following the episode of AIAW.

Figure 2 Source of information for patients with dystroglycanopathy

AIAW = acute illness-associated weakness.

summarizes the source of information for the patients with AIAW. We were able to review medical records or hospitalization notes for 12 of the 21 patients (57.1%). See the supplementary data for case reports (appendix e-1, figure e-1, video 1, video 2).

Most patients reported 1 episode of AIAW, but 7 patients (33%) reported experiencing multiple episodes; these reported 1 major episode of weakness followed by a few less severe episodes throughout childhood, all associated with a febrile illness. Patients with repeat episodes of AIAW all had their first episode before age 6; however, not all children who

had a first AIAW at <6 years old had recurrent episodes. Age at first episode ranged from 3 months to 38 years, with a median age of 2 years (IQR 1–6.5 years). Seventeen of the 21 (81%) patients were 7 years old or younger at the time of AIAW (figure 3). Ten patients (47.6%) were diagnosed with muscular dystrophy after the episode of AIAW, 1 had delayed motor milestones prior to AIAW, and the remainder were asymptomatic. A few of these patients underwent extensive testing for metabolic myopathy or treatment for myositis before muscular dystrophy was suspected.

The episodes of weakness were associated with specific loss of previously achieved motor function. Young children experienced loss of head control or ability to sit unassisted, while older individuals typically lost the ability to walk. All patients except one recovered to their previous level of function. Recovery time ranged from 2 days to months; the median time to recovery was 8.25 days.

Creatine kinase (CK) level was checked during the AIAW for 10 patients (47.6%), and the mean was 17,068 U/L (SD $\pm$ 12,240.1; range 600–31,600 U/L). Two CK levels were reported as “too high to measure” and were not included in the calculation of the mean. We have data on follow-up CK levels (mean 2,503 U/L; SD $\pm$ 15,055.4; range 800–4,000 U/L) for 5 patients, obtained 3–12 weeks following initial CK. For these 5 patients (patients 3, 8, 9, 10, 20), the CK level decreased by a mean of 20,245 U/L (SD $\pm$ 612.4; range 7,146–29,083 U/L).

Patients experiencing AIAW in this cohort had pathologic variants in *FKRP* (14 patients [67%]), *FKTN* (3 [14%]), *POMGNT1* (1 [5%]), *POMT1* (1 [5%]), and *POMT2* (2 [10%]). Four of the 14 patients with *FKRP* mutations were homozygous for the founder mutation, c.826C>A, and the remainder were compound heterozygotes. The distribution of genotypes represented in those with AIAW did not significantly differ from those surveyed who did not experience AIAW (68% *FKRP*, 5% *FKTN*, 5% *POMGNT1*, 5% *POMT1*, and 8% *POMT2* variants; Pearson χ^2 exact analysis, $p = 0.642$).

Details about the associated febrile illness were often vague and even review of medical records simply reported a viral illness. Information about specific symptoms in addition to fever was available for 13 of the 21 patients. Twelve of the 13 patients had symptoms involving the respiratory system (sore throat or cough), and the other patient reported a gastrointestinal illness. A causative pathogen was identified in 4 of the 21 patients (H1N1, coxsackievirus, respiratory syncytial virus (RSV), and streptococcus). The majority of patients developed weakness within 3 days of becoming ill. Eleven of 21 (52.4%) patients were

Figure 3 Age at first episode of acute illness-associated weakness (AIAW) in patients with dystroglycanopathy (DG)

Age at first episode of AIAW in patients with DG, with a line at the median age (8 years) and error bars at the interquartile range (1.1 and 6.5 years).

hospitalized during the AIAW, and one patient required intubation due to respiratory failure. Other complications experienced by hospitalized patients were respiratory distress, hypoxia with possible aspiration, febrile seizure, and one patient was diagnosed with viral meningitis. No patient had clinically identified cardiomyopathy associated with the AIAW. Six patients received antibiotics and 3 received a steroid burst for the AIAW. Two patients (patients 15 and 19) was already on steroids prior to AIAW, and steroids were not increased during AIAW.

AIAW in patients with DBMD. Surveys were mailed to 187 patients with DBMD, and 51 (27.3%) surveys were completed. The median age of those who completed the survey was 14 years (IQR 7–22 years) and 15 years (IQR 8–26 years) for those who did not return the survey ($p = 0.694$). Seventeen patients with DBMD (33%) reported acute weakness; however, only 2 (4%) met our criteria for AIAW. The remaining 15 patients did not meet the criteria of AIAW because they reported weakness following surgery ($n = 4$), stress (5), throughout life (4), every time he got sick (1), and weakness greater than 7 days after becoming ill (1).

The 2 patients with DBMD who had AIAW were both 3 years old at the time of event. One patient lost the ability to walk and hold his head up hours after contracting strep throat and influenza. The other patient lost the ability to walk, run, and lift objects 2–3 days following a febrile illness with symptoms of diarrhea, vomiting, and a cough. Both patients were seen by a physician following this episode, were treated with antibiotics, and fully recovered within 1 week.

Comparison of frequency of AIAW between patients with DG and patients with DBMD. To compare the frequencies of AIAW in DG compared to DBMD, we used only survey data. A significantly higher percentage of patients with DG (56.5%) responded to the survey than patients with DBMD (27.3%) ($p < 0.01$). Within those who completed surveys, significantly more AIAW was reported in the DG cohort (23%) than in the DBMD cohort (4%) (OR 7.35, 95% CI 1.55, 34.77; $p = 0.005$). When adjusted for age, an even greater effect was observed, with AIAW OR of 9.93 (95% CI 2.02, 48.90; $p < 0.01$) for the DG cohort relative to the DBMD cohort.

DISCUSSION In our cohort of individuals with DG, approximately 20% had AIAW. Others have described this phenomenon and the clinical characteristics in our series are similar to what has been reported in a single series or in case reports.^{4–12,14} We found this phenomenon typically occurs in children who are <7 years old; others have reported it in patients between 3 months and 9 years old.^{4–12,14}

The DG-associated AIAW is often striking enough to result in hospitalization.^{4,5} Respiratory distress is a common occurrence and can require intubation (our patient 16)^{4,5} or result in death,⁵ demonstrating the importance of monitoring respiratory status. Weakness is associated with high CK and recovery to baseline function in most cases over 1–3 weeks.⁵

In our series, 5 DG genes (*FKRP*, *FKTN*, *POMGNT1*, *POMT1*, and *POMT2*) were represented in the group with AIAW, and the distribution of genes was consistent with the overall distribution in our cohort of patients with DG. AIAW was previously associated primarily with *FKTN* mutations, but case reports describe it in patients with *ISPD*, *GMPPB*, and *FKRP* variants.^{4–12,14,15} We found a significantly lower frequency of AIAW among patients with DBMD. Thus, our results together with the literature suggest that this phenomenon occurs preferentially in the DGs, independent of genotype.

Half of our patients were not known to have muscular dystrophy at the time of AIAW, consistent with published cases.^{7–10,12} The differential diagnosis is broad when a previously healthy child presents with generalized weakness of rapid onset and an elevated CK (>1,000 IU/L) (reviewed in reference 16). The most common diagnosis is viral myositis. CK levels are elevated in patients with benign acute childhood myositis, but these levels return to normal within a few weeks.^{16–18} Patients with DG who experience AIAW will have acute elevation of CK (usually >10× normal in our series), then have lower but persistent CK elevation in a range typically >5× normal. Patients with acute viral myositis often report myalgias as their chief complaint^{16–18}; calf pain can result in refusal to walk^{16–18} without frank weakness. In contrast, patients with DG have clear weakness with loss of motor function. Thus it is important to attempt to distinguish pain from weakness, and to follow CK levels once symptoms have resolved.

Steroids have been proposed to shorten the course of AIAW in the DGs. Three of the patients in our cohort received a steroid burst during their AIAW, but it is unclear from our retrospective data if steroids were beneficial. One case study described a patient with DG who lost the ability to stand following a febrile illness. Following administration of steroids, she rapidly improved and was able to stand within 3 days of treatment.⁷ In a series of patients with FCMD, there was a tendency for patients given steroids to have a shorter recovery time; however, the results did not reach statistical significance.⁵

The mechanism of AIAW in patients with DG is not understood. It is possible that muscles are directly invaded by viruses, or that muscle cells with a defect in glycosylation have an increased viral affinity.⁵ Glycosylated α -DG is the cellular receptor for old world

arenaviruses, including lymphocytic choriomeningitis virus (LCMV), Lassa fever virus, and *Mycobacterium leprae*.² Lassa fever virus and *Mycobacterium leprae* are unlikely to play a role in pathogenesis in our cases. Infection with LCMV in childhood can cause a brief, nonspecific illness that can include aseptic meningitis.¹⁹ LCMV competes with extracellular matrix proteins for α -DG binding, and binding of inactivated LCMV results in membrane destabilization.²⁰ Thus, it is possible that in some cases the AIAW is a direct result of viral disruption of the sarcolemma. However, the organisms reported to be associated with AIAW (H1N1, coxsackievirus, RSV, and streptococcus in our series; coxsackievirus, echovirus, enterovirus⁵) are not known to interact directly with α -DG. It is possible that patients with DG, with destabilized cellular membranes due to hypoglycosylation of α -DG, are at risk for more severe injury as a result of myositis from usual childhood viruses. However, if this were the sole mechanism of the phenomenon of AIAW, we would expect it to be seen in all patients with muscular dystrophy due to a disruption in the dystrophin glycoprotein complex, and our results (and clinical experience) demonstrate a higher incidence in patients with DG over other forms of muscular dystrophy like DBMD. The recent observation of a myasthenic phenotype in patients with DG due to *GMPPB* mutations raises the possibility of impaired neuromuscular transmission causing weakness.¹⁵ Glycosylated α -DG is known to play a role in stabilization of the acetylcholine receptor^{21,22} and infection is a common precipitant of myasthenic crisis.²³ However, to date, the myasthenic syndrome has only been reported in mildly affected individuals with mutations in *GMPPB*, so it might not be a general DG phenomenon. Furthermore, the elevation of CK associated with weakness would not be explained by this mechanism. Finally, the phenomenon of illness-associated weakness could reflect a more general maladaptive response at the level of muscle membrane to stress or fever.

The reason for AIAW preferentially affecting young children is also unclear. Possible factors include initial exposure to many viruses and the propensity to develop high fevers. Additional work is needed to understand the mechanism underlying the clinical observations.

Limitations of this study include the fact that we were not able to review all medical records and were dependent on patient recall for some patients. In addition, the survey response rate in the DBMD cohort was low; however, the DBMD responders were representative of the whole group as tested by age. Among the DG group, survey respondents were older than the nonresponders. This difference is more likely to result in a failure to recall acute episodes of weakness in early

childhood, thus our results might represent a lower estimation of the frequency of the phenomenon.

Clinicians should be aware of this phenomenon of AIAW in people with DG and follow the CK level of patients with presumed viral myositis after resolution of symptoms. Steroids might be beneficial in shortening the course of weakness, but further studies are needed on the effectiveness of this treatment. Clarification of the mechanism underlying this observation will be of interest in furthering our understanding of the biology of the DGs.

AUTHOR CONTRIBUTIONS

C.R. Carlson: acquisition of data, analysis and interpretation of data, drafting/revising the manuscript for content. Dr. McGaughey: analysis and interpretation of data, drafting/revising the manuscript for content. Dr. Eskuri: acquisition of data, critical review of manuscript. C.M. Stephan: coordination of trial, acquisition of data, critical review of manuscript. Dr. Zimmerman: analysis and interpretation of data, drafting/revising the manuscript for content. Dr. Mathews: concept development, acquisition of data, analysis and interpretation of data, drafting/revising the manuscript for content.

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DISCLOSURE

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