Original Article

A study of acute muscle dysfunction with particular reference to dengue myopathy

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Abstract

Background: Acute myopathy is a common cause of acute motor quadriparesis which has various etiologies with different courses of illness and prognosis depending on the cause. Understanding this diversity helps us in proper approach toward diagnosis, predicting the prognosis, and possible complications and in improving the treatments that are being provided. This study was planned to study the clinical, electrophysiological, and etiological profile of patients presenting with acute myopathy. We also studied how dengue-related acute myopathy differs from other causes and also difference between myopathy due to myositis and hypokalemia in cases of dengue. **Materials and Methods:** This was a prospective, observational study involving all clinically suspected cases of acute myopathy of not more than 4 weeks duration with raised serum creatine kinase (CK) level. They were subjected to detailed clinical evaluation along with hematological, biochemical, microbiological, and electrophysiological studies and followed-up for outcome at 1 and 3 months. Muscle biopsy and histopathological examination were done in selected patients after taking informed consent. Statistical analysis was performed by appropriate methods using SPSS version 16.0 (Chicago, IL, USA). **Results:** We evaluated thirty patients of acute myopathy with raised CK level. Seventeen patients had fever, 11 had myalgia, and 5 had skin lesions. All presented with symmetric weakness, 17 (56.7%) patients having predominantly proximal weakness, neck or truncal weakness in 6 (20%), hyporeflexia in 12 (40%), with mean Medical Research Council (MRC) sum score of 46.67 ± 6.0. Eight (mean modified Barthel index [MBI] at presentation - 15 ± 3.7) patients had poor functional status according to MBI and 15 according to modified Rankin scale (MRS) (mean MRS score - 2.5 ± 1.2). Etiology was dengue viral infection in 14 patients; hypokalemia due to various causes other than dengue in 8; pyomyositis in 3; dermatomyositis, polymyositis, thyrotoxicosis, systemic lupus erythematosus, and unknown etiology in one each. Only eight patients had abnormal electrophysiology and seven among nine biopsies done were abnormal. At 1 month, 24 (80.0%) and 23 (76.7%) patients had achieved normal MBI and MRS scores with 28 (93.3) and 27 (90%) patients, respectively, at 3 months. Dengue with hypokalemia had less myalgia, more of hyporeflexia, and lower serum CK compared to those without hypokalemia. **Conclusion:** Dengue infection and hypokalemia due to various causes are the most common causes of acute myopathy and are associated with rapid and complete recovery within 1 month. Shorter duration of illness, higher MRC sum score, better disability status at presentation, lower serum CK correlate with better outcome. Biopsy was decisive in <20% cases; hence, it is not primary investigation in acute myopathy.

Key Words

Acute myopathy, dengue myositis, electrophysiology, muscle histopathology

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Introduction

Disorders of skeletal muscle encompass a variety of illnesses that cause weakness, pain, and fatigue in any combination.

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Myopathy simply refers to an abnormality of the muscle and has no other connotation. Myopathy term many a times is used interchangeably with myositis. Myositis is defined as inflammation of muscle, especially a voluntary muscle, characterized by pain, tenderness, swelling, and/or weakness.[1] Myositis implies an inflammatory disorder and is usually reserved for disorders, in which the muscle histology shows an inflammatory response.[2] However, histopathological confirmation cannot be obtained in all cases despite the evidence of muscle damage in the form of elevated muscle enzymes. The muscle biopsy may not be done due to its invasive nature or transient and benign nature of some myopathies not warranting biopsy, especially in the presence of obvious cause and typical presentation. Other investigations such as nerve conduction studies (NCSs) and electromyography (EMG) may aid in both confirming muscle disease as the source of weakness and also in ruling out neurogenic causes of acute muscle dysfunction. In such cases where there is no histopathological evidence but there is other evidence of muscle involvement, the term myopathy or muscle dysfunction can be used instead of myositis.

Acute myopathy or myositis is one of the common differential diagnoses of acute motor quadriparesis among various others. Although myopathy usually is considered to have subacute to chronic presentation of weeks to months, some cases may have acute presentations in days to weeks. The clinical signs and symptoms too differ compared to chronic myopathy in terms of fever, myalgia, absence of atrophy, weakness distribution, symmetry of weakness, associated symptoms such as skin changes and joint pains.

The spectrum of acute myopathy includes various etiologies with different pathophysiology. The different etiologies of acute myopathy include infection, electrolyte disturbances, autoimmune conditions, genetic disorders, medication adverse events, and diseases of the endocrine system.[1] Pathogens such as bacteria, fungi, parasites, and viruses may lead to infectious cause of acute myositis with virus and bacteria contributing most of the cases. Influenza virus is the most common cause of benign acute myositis commonly occurring in winters and in children.[3] Whereas in countries where dengue is endemic, dengue-induced acute muscle dysfunction is one of the major causes, especially during rainy season due to increased breeding of mosquitoes.[4] Among bacteria, *Staphylococcus aureus* causing pyomyositis is one of the most common causes presenting acute to subacute with muscle pain, swelling, or indurations with or without weakness.[5] Other than virus and bacteria, fungi and parasites can also present with myositis, especially cysticercosis in muscle. Electrolyte imbalances can also present with pure muscle weakness ranging from acute to chronic presentations. Certain electrolyte derangements are among the most common causes of myopathy, the most important being deficiencies of potassium and phosphorus. Profound electrical disturbances without serious derangements of muscle cell composition may be seen in disorders such as hyperkalemia and hypocalcemia. However, most serious electrolyte disorders cause evidence of both muscle and nerve dysfunction, especially if the evaluation includes measurements of electrical activity, such as EMG and nerve conduction velocity.[6]

Apart from infectious and electrolyte disturbances, acute muscle dysfunction can occur due to endocrinopathies such as thyrotoxicosis, hypothyroidism, pheochromocytoma, and Cushing's syndrome; autoimmune conditions such as polymyositis and dermatomyositis; genetic causes such as periodic palsies; medications; and toxins.[6-8]

Electrodiagnostic (EDX) studies are more commonly an extension of clinical assessment and planned based on the clinical findings and differentials. Their main use in a case of suspected cause of myopathy is to rule out the neural or neuromuscular cause of weakness and to narrow down the differentials based on some specific findings such as spontaneous activities. NCSs mostly help in showing whether there is nerve involvement in the form of any abnormality in sensory nerve action potential (SNAP), prolonged distal latency or reduced velocity in compound muscle action potential (CMAP), or temporal dispersion or conduction block. EMG plays more important role among EDX in a case of suspected case of myopathy. It is more sensitive in identifying myopathic cause of weakness. Short duration, reduced amplitude, and polyphasic muscle unit action potentials (MUAPs) with early recruitment and complete interference pattern suggest myopathic nature of weakness. It can also help in narrowing differentials by the presence of spontaneous activities such as fibrillation, positive sharp waves, or myotonia, which are seen in select few causes with muscle membrane irritability such as inflammatory and toxic myopathies. The role of these studies in a case of acute myopathy under evaluation is not well established. There are studies that have reported EDX changes in infectious causes such as dengue, influenza, pyomyositis; electrolyte disturbances; and inflammatory causes.[4,9-11] EMG may not be needed in all cases of chronic myopathy as much information may not be gained other than nonspecific finding of myopathic changes or may be normal in some cases of myopathies such as endocrine or metabolic causes. Further, other ancillary tests such as genetic analysis may help in confirming the diagnosis in a clinically suspected case. Or in those cases where biopsy is anyway required for the diagnosis, EMG may not be additive in providing information. Hence, what role does EDX and specifically EMG play in evaluation of cases of acute myopathy and is there any different pattern was also studied in this study.

As there is a lack of studies prospectively evaluating cases of acute myopathy, we planned this study with the aim to evaluate clinical profile, EDX findings, and etiological spectrum in cases of acute myopathy. Our other aims were to study the prognosis in the form of disability at 1 and 3 months and what baseline factors correlated with baseline severity and good prognosis at 1 and 3 months.

Materials and Methods

This prospective, observational study was conducted at the Department of Neurology, King George Medical University, Lucknow, in collaboration with the Department of Microbiology, Plastic Surgery of King George Medical University, Lucknow, and Department of Pathology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow. The study subjects were enrolled from August 2013 to October 2015. Written informed consent was obtained from every individual

or their guardian before being enrolled in the study. The study was approved by the Institutional Ethical Committee. Flow diagram of the study is presented in Figure 1.

Inclusion criteria

All patients admitted to the neurology department with symptoms of acute muscle weakness of <4 weeks duration with raised serum creatine kinase (CK) level (above upper limit of normal [ULN] [195 IU/L]) over the study period of August 2013 to October 2015 were included in the study.

Exclusion criteria

Patients with either NCS not consistent with muscle disease (findings apart from reduced CMAP) or EMG suggestive of neuropathic pattern (large amplitude long duration motor unit action potentials with fasciculations, reduced recruitment, or incomplete interference) were excluded from the study.

Evaluation

Detailed clinical history and physical examination were done in all patients. The weakness was graded according to Medical Research Council (MRC) scale. MRC sum score (MSS) was calculated as sum of overall power at bilateral shoulder, elbow, wrist, hip, knee, and ankle, with score of 60 being maximum power and 0 being complete weakness. Weakness was also labeled as either distal, proximal, or both proximal and distal based on involvement of proximal and distal musculature. Disability assessment was done as per modified Barthel index (MBI) (20-point scoring system with higher points signifying better functional status). Baseline disability was defined as poor functional status based on MBI ≤12.

Investigation

The laboratory investigations including complete blood count, liver and kidney function tests, serum sodium, serum potassium, blood sugar, and serum CK were done in all acute myopathy cases. Serum potassium of ≤3.5 mEq/L was taken as hypokalemia. Total leukocyte counts of <4000 cells/μl was considered as leukopenia and >11,000 cells/μl was considered as leukocytosis. Platelet count of $<1.5 \times 10^6$ cells/μl was considered as thrombocytopenia. Thyroid function test, erythrocyte sedimentation rate (ESR), C-reactive protein, anti-nuclear antibody (ANA), rheumatoid factor, and blood culture/sensitivity were done according to the clinical scenario. Virological studies for human influenza virus, dengue virus, cytomegalovirus, Epstein–Barr virus, *Enterovirus*, human immunodeficiency virus, hepatitis B surface antigen, and hepatitis C virus were also done according to the clinical settings.

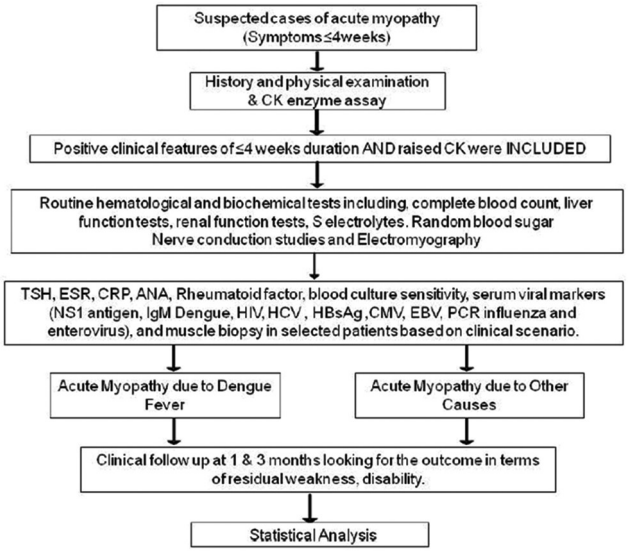

Figure 1: Plan of study

Electrophysiological evaluation

NCSs and EMG of all four limbs were done using standard techniques in all patients, which included motor studies of bilateral ulnar, median, posterior tibial, and common peroneal nerves and sensory studies of bilateral ulnar, median, and sural nerves. Muscles for EMG study were selected according to clinical scenario with at least one clinically normal and abnormal muscle sampled. Patients whose NCS showed prolonged distal latency, reduced conduction velocity of CMAP, conduction block, or abnormal SNAP were excluded from the study. The patients with large amplitude,long duration MUAPs, fasciculations, reduced recruitment and incomplete interference suggestive of neuropathic pattern on Electromyography were also excluded from this study.

Muscle biopsy

Muscle biopsy was done after taking informed consent and only in selected patients after considering the indications and contraindications for the procedures. The procedure was done in the Department of Plastic Surgery, King George Medical University, under local anesthesia in sterile aseptic condition. Two muscle tissue samples from moderately weak muscle, preferable right vastus lateralis were collected one sample each in a saline-soaked gauge and sterile container containing formalin. The samples were sent to the Department of Pathology, Dr. Ram Manohar Lohia Institute of Medical Sciences, on the same day of biopsy procedure for fixation and staining. Necessary precautions were taken before, during, and after the procedure to prevent any untoward complication.

Treatment

Standard treatment was given to every patient according to the cause of myopathy after the initial investigations to look for the etiology.

Follow-up and assessment of outcome

All patients were followed up at 1 and 3 months for repeat clinical history and physical examination along with disability assessment as per MBI with poor outcome defined as MBI ≤12 at 1 and 3 months.

Statistical analysis

Statistical analysis was performed using the Statistical Package of Social Sciences (SPSS) version. 16.0 (Chicago, IL, USA). Categorical variables are expressed as percentages and continuous variables are expressed as means ± standard deviation. Chi-square test or Fisher's exact test was used to compare qualitative variables as applicable. Independent

sample *t*-test and ANOVA were used to compare means as applicable. Spearman's correlation was used for correlation coefficient. A $P < 0.05$ was considered statistically significant.

Results

Thirty-two patients were included in the study based on the predefined inclusion criteria. Two of them were excluded as they had NCS not compatible with myopathy. The baseline demographic, clinical features, and investigations of all thirty patients (twenty males, ten females) are shown in Table 1. The mean age of the study population was 29.3 ± 11.5 years, with mean duration of symptoms being 6.4 ± 7.3 (range: 1–25) days.

Clinical features

Apart from weakness, fever (17) was the most common associated symptom with other symptoms being muscle pain (11), muscle swelling (2), and skin lesions (5). Weakness was symmetrical in all with pure proximal weakness more compared to proximal and distal weakness and five patients had weakness of neck and truncal muscles also. Mean MSS was 46.67 ± 6.0 ranging from 28 to 54. Hyporeflexia or areflexia was seen in 12 patients. Eight patients had poor functional status according to MBI. None of the patients had renal failure.

Investigations

Complete blood count revealed thrombocytopenia in 12, leukopenia in 7, leukocytosis in 6, and relative lymphocytosis in 10. Mean serum CK level was 3158.2 IU/L with 3–10 times above ULN in 10 and more than 10 times in 11. Hypokalemia was seen in 13, elevated ANA in 4, anti-Ro in 1, thyroid function tests suggesting hyperthyroidism in two and hypothyroidism in one. Blood culture was positive for *S. aureus* in three patients of acute bacterial myositis.

EMG showed myopathic changes in all patients with many showing only mild myopathic changes in the form of short to normal amplitude, short duration, polyphasic MUAPs. Spontaneous activity in the form of fibrillation and positive sharp waves in EMG was seen in eight patients (three cases of pyomyositis and one each of dengue with hypokalemia, dengue without hypokalemia, dermatomyositis, polymyositis, and myopathy secondary to systemic lupus erythematosus [SLE]). NCS was abnormal in only two patients showing only reduced amplitudes of CMAPs.

Dengue infection (14 patients) was the most common etiology with dengue nonstructural protein 1 (NS1) antigen positivity in 7 patients, IgM antibody against dengue virus in 3 patients, and both dengue NS1 antigen and IgM antibody against dengue in 4 patients. Hypokalemia (13 patients) was the next most common etiology, which included five cases of dengue virus infection, three cases of probable hypokalemic periodic palsy. There was one case each of renal tubular acidosis, renal tubular acidosis secondary to Sjogren's syndrome, hyperthyroidism, acute pancreatitis, and drug-induced causing hypokalemia. Other etiologies included acute bacterial myositis (3), dermatomyositis (1), polymyositis (1), myopathy secondary to SLE (1), hyperthyroidism without hypokalemia (1), and unknown cause (1).

Table 1: Baseline demographic, clinical features, disability status, and investigation profile of thirty patients of acute myopathy

Variable	Mean±SD (range) or *n* (%)
Age (years)	29.3±11.5 (10-50)
Sex	
Male	20 (66.7)
Female	10 (33.3)
Duration of symptoms (days)	6.4±7.3 (1-25)
Fever	17 (56.7)
Muscle pain	11 (36.7)
Muscle swelling	2 (6.7)
Skin lesions	5 (16.7)
Weakness	
Proximal only	17 (56.7)
Proximal and distal	13 (43.3)
Neck or truncal weakness	5 (16.7)
MRC sum score (0–60)	46.67±6.0 (28-54)
DTRs	
Normal	18 (60)
Hyporeflexia	12 (40)
MBI at presentation	15±3.7 (7-20)
Good (>12)	22 (73.3)
Poor (□12)	8 (26.7)
Total hemoglobin (gm/dl)	12.8±1.9 (8.2-16.6)
PCV (%)	42.6±4.9 (32.0-52.0)
Platelet count (×10^3 cells/μl)	183±148 (25–737)
Thrombocytopenia (<150×10^3 cells/μl)	12 (40)
Total leukocyte count (cells/μl)	8283.7±6684.8 (2700-37,480)
Normal (4000–11,000)	17 (66.7)
Leukocytopenia (<4000)	7 (23.3)
Leukocytosis (>11,000)	6 (20.0)
Relative lymphocyte (%)	29.67±10.3 (10-49)
Relative lymphocytosis (>35%)	10 (33.3)
Total serum CK (IU/L)	3158.2±4668.6 (240.0-18,540.0)
<3 times ULN	9 (30.0)
3–10 times ULN	10 (33.3)
>10 times ULN	11 (36.7)
AST (IU/L)	184.3±213.9 (18-870)
ALT (IU/L)	90.3±112.2 (10.6-536.0)
Serum potassium (mmol/L)	3.48±0.9 (1.3-5.0)
Hypokalemia (<3.5 mmol/L)	13 (43.3)
TSH (μIU/ml)	3.05±1.3 (0.05-7.0)
Normal	27 (90.0)
Low	2 (6.7)
High	1 (3.3)
ESR (mm in 1 h)	20.8±13.3 (9-80)
ANA	
Negative	26 (86.7)
Positive	4 (13.3)
Electrophysiology	
Abnormal NCS	2 (6.7)
Myopathic EMG	22 (73.3)

Contd...

Table 1: Contd...

Variable	Mean±SD (range) or *n* (%)
Myopathic EMG with spontaneous activity	8 (26.7)
Muscle biopsy	
Not done	24
Normal	2
Abnormal	4
Etiology	
Dengue with hypokalemia	5 (16.7)
Dengue without hypokalemia	9 (30.0)
Hypokalemia due to other causes	8 (26.7)
Pyomyositis	3 (10.0)
Polymyositis/ dermatomyositis	2 (6.7)
Others	3 (10.0)

MRC = Medical Research Council, DRTs = Deep tendon reflexes, MBI = Modified Barthel index, PCV = Packed cell volume, CK = Creatine kinase, ULN = Upper limit of normal, AST = Aspartate aminotransferase, ALT = Alanine transaminase, TSH = Thyroid-stimulating hormone, ESR = Erythrocyte sedimentation rate, ANA = Anti-nuclear antibody, NCS = Nerve conduction studies, EMG = Electromyography, SD = Standard deviation

Muscle biopsy was done in six patients, which was normal in two (who included patients of dengue virus infection) and abnormal in four (dermatomyositis [1], polymyositis [1], myopathy secondary to SLE [1], and unknown cause [1]). Biopsy was done in those cases where the diagnosis was not made after initial investigations or in cases who presented with long duration symptoms.

Patients of acute dengue infection

Out of total thirty patients, 14 were positive for either dengue NS1 antigen and/or IgM antibody against dengue virus. Of this, five had hypokalemia and nine had normokalemia. When patients of dengue were compared with patients without dengue infection; fever (P = 0.001), hyporeflexia (P = 0.02), leukopenia (P = 0.04), relative lymphocytosis (P = 0.00), and thrombocytopenia (P = 0.001) were significantly more common with significantly shorter duration of symptoms (P = 0.04), lower platelet count (P = 0.001), lower total leukocyte count (TLC) (P = 0.01), and higher lymphocyte percentage (P = 0.001) in patients with dengue infection [Table 2]. On comparing patients of dengue with hypokalemia with those of dengue without hypokalemia, hyporeflexia (P = 0.09), serum CK <10 times (P = 0.01), and leukopenia (P = 0.09) were more common in dengue with hypokalemia while serum CK >10 times (P = 0.01) and thrombocytopenia (P = 0.03) were more common in dengue without hypokalemia. Furthermore, in patients of dengue with hypokalemia, total serum CK level (P = 0.08) and TLC (0.07) were lower and platelet count (0.03) was higher compared to those without hypokalemia [Table 3].

Correlation studies

Baseline severity in the form of MSS and MBI at presentation did not show any correlation with baseline clinical or investigation parameters which included age, duration of symptoms, MSS, serum CK, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum potassium, ESR, packed cell volume, platelet count, total leukocyte count, and relative lymphocyte percentage. While in patients with dengue infection, serum potassium showed significant positive correlation with MSS (P = 0.03, r = 0.58), suggesting that lower potassium level correlates with more severe weakness at presentation.

Disability outcome at 1 and 3 months

Clinical outcome was assessed at 1 and 3 months by MBI. Only one patient had full MBI score at presentation. At 1 month, 24 patients attained full MBI score while all except two attained it by the end of 3 months. One death occurred (acute myopathy of unknown cause) at the end of 1 month and none thereafter at 3 months follow-up. No patients had MBI ≤12 at 1 and 3 months follow-up with lowest MBI of 17 at 1 month follow-up and 18 at 3 months.

Among baseline clinical and investigation parameters, MSS, MBI0, and relative lymphocyte percentage showed significant positive correlation, and duration of symptoms, AST, ALT, ESR, platelet count, and TLC showed significant negative correlation with MBI at 1 month and 3 months when studied in all thirty patients [Table 4].

Discussion

Acute myopathy is poorly defined entity that can be caused by various etiologies with different manifestations that need to be approached differently compared to common chronic myopathies. Although there are studies describing different etiologies causing acute myopathy, prospective study analysis of acute myopathy as a whole is lacking in literature. This is the first study according to best of our knowledge which has tried to look in this aspect.

Of the total thirty patients studied, two-third of them were males with mean age in the younger age group 29.3 ± 11.5 years, ranging from 10 to 50 years. Although the duration of symptoms in inclusion criteria was <4 weeks, majority of the patients presented within 1st week of symptom onset with the mean duration of 6.4 days. Clinical features of acute myopathy patients in this study were similar to those of more commonly seen chronic myopathy with symmetric proximal weakness in all patients. One-third patients showed distal weakness and five patients showed neck and truncal weakness. However, unlike chronic myopathy, fever was frequently seen in more than half of the patients and myalgia was the second most common associated symptom seen in one-third of patients studied. Furthermore, patients had muscle swelling rather than atrophy that is commonly seen in chronic myopathy. Hyporeflexia was also more frequent in acute myopathy (40%), which is usually late feature in chronic myopathy when there is marked atrophy of muscles. Hyporeflexia is commonly seen in anterior horn cell disorder, radiculopathy, or neuropathy with usually late finding in myopathy when loss of muscle bulk leads to reflex loss. Such high presence of hyporeflexia in acute cases as seen in this study indicates cause other than just loss of muscle bulk. It is seen that acute myopathy due to viral myositis or electrolyte imbalance can have early loss of reflexes due to reduced excitability of the muscle fibers.[4,6,12-15]

Table 2: Comparison of demographic, clinical features, disability status, blood investigations, and electrophysiology findings between patients with and without dengue infection

Variable	Dengue (*n*=14)	Nondengue (*n*=16)	*P*	OR (CI)
Age (years)	30.57±8.5	28.19±13.8	0.57	
Sex				
Males (*n*)	11 (78.6)	9 (56.3)	0.26	
Female (*n*)	3 (21.4)	7 (43.8)		
Duration of symptoms (days)	3.50±1.1	8.94±9.4	0.04	
Fever	13 (92.9)	4 (25.0)	0.001	39.0 (3.8–399)
Muscle pain	6 (42.9)	5 (31.3)	0.71	
Muscle swelling	0	2 (12.5)	0.49	
Skin lesions	4 (28.6)	1 (6.3)	0.16	
Weakness				
Proximal only	6 (42.9)	11 (68.8)	0.27	
Proximal and distal	8 (57.1)	5 (31.3)		
Neck or truncal weakness	2 (14.2)	3 (18.8)	0.73	
MRC sum score (0-60)	45.86±5.7	47.38±6.2	0.50	
DRTs				
Normal	5 (35.7)	13 (81.3)	0.02	7.8 (1.5–41.2)
Hyporeflexia	9 (64.3)	3 (18.8)		
MBI at presentation				
Good (>12)	9 (64.3)	13 (81.3)	0.42	
Poor (□12)	5 (35.7)	3 (18.8)		
Total serum CK (IU/L)	3411.98±4236.7	2936.13±5144.8	0.79	
<10 times ULN	7 (50.0)	12 (75.0)	0.26	
>10 times ULN	7 (50.0)	4 (25.0)		
AST (IU/L)	197.64±204.5	172.63±227.8	0.76	
ALT (IU/L)	95.82±91.2	85.54±130.7	0.81	
Serum potassium (mmol/L)	3.60±0.9	3.37±0.9	0.48	
ESR (mm in 1 h)	16.00±5.1	24.94±16.7	0.06	
Electrophysiology				
Normal	12 (85.7)	10 (62.5)	0.23	
Abnormal NCS	2 (14.3)	0		
Abnormal EMG	2 (14.3)	6 (37.5)		
Abnormal NCS or EMG	2 (14.3)	6 (37.5)		
Total hemoglobin (g/dl)	13.34±2.2	12.34±1.4	0.14	
PCV (%)	43.39±4.5	41.99±5.3	0.45	
Platelet count (×10^3 cells/μl)	90.71±58.2	264.38±156.1	0.00	
Thrombocytopenia (<150×10^3 cells/μl)	11 (78.6)	1 (6.3)	0.00	55 (5–602.2)
Total leukocyte count (cells/μl)	4958.57±2472.5	11,193.13±7857.0	0.01	
Normal (400–11,000)	7 (50.0)	10 (62.5)	0.04	
Leukocytopenia (<4000)	6 (42.9)	1 (6.3)		
Leukocytosis (>11,000)	1 (7.1)	5 (33.3)		
Relative lymphocyte (%)	37.00 (6.8)	23.25±8.5	0.00	
Relative lymphocytosis (>35%)	9 (64.3)	1 (6.3)	0.00	27 (2.7–269.5)
Dengue serology				
NS1	7 (50.0)	NA	NA	NA
IgM antibody	3 (21.4)			
Both positive	4 (28.6)			

MRC = Medical Research Council, DRTs = Deep tendon reflexes, MBI = Modified Barthel index, PCV = Packed cell volume, CK = Creatine kinase, ULN = Upper limit of normal, AST = Aspartate aminotransferase, ALT = Alanine transaminase, ESR = Erythrocyte sedimentation rate, NCS = Nerve conduction studies, EMG = Electromyography, CI = Confidence interval, OR = Odds ratio, NS1 = Nonstructural protein 1, NA = Not available

In investigation profile, mean serum CK level was 3158 IU/L, ranging from 240 IU/L to 18540 IU/L. One-third had more than ten times rise in CK, one-third 3–10 times, and the rest <3 times rise. This increase in muscle enzymes suggests structural damage rather than just functional impairment as the cause of weakness in our study patients. Raised CK is commonly seen in viral myositis, acute bacterial myositis, rhabdomyolysis, drug- and toxin-induced myopathy, while it is less common in pyomyositis, parasitic or fungal myositis, electrolyte- and endocrine-related myopathy, except for severe hypokalemia and hypothyroidism.[7,8,15-17]

Table 3: Comparison of demographic, clinical features, disability status, blood investigations, and electrophysiology findings between patients of dengue infection and hypokalemia and dengue infection without hypokalemia

Variable	Dengue without hypokalemia (*n*=9)	Dengue with hypokalemia (*n*=5)	*P*
Age (years)	28.44±7.1	34.4±10.2	0.22
Sex			
Males (*n*)	8 (88.9)	3 (60.0)	0.51
Female (*n*)	1 (11.1)	2 (40.0)	
Duration of symptoms (days)	3.56±1.1	3.40±1.1	0.81
Fever	9 (100)	4 (80)	0.36
Muscle pain	5 (55.6)	1 (20.0)	0.30
Muscle swelling	0	0	-
Skin lesions	4 (44.4)	0	0.22
Weakness			
Proximal only	4 (44.4)	2 (40.0)	1.0
Proximal and distal	5 (55.6)	3 (60.0)	
Neck or truncal weakness (%)	1 (20)	1 (20)	-
MRC sum score (0–60)	47.11±5.4	43.60±6.3	0.29
DRTs			
Normal	5 (55.6)	0	0.09
Hyporeflexia	4 (44.4)	5 (100.0)	
MBI at presentation			
Good (>12)	7 (77.8)	2 (40.0)	0.27
Poor (□12)	2 (22.2)	3 (60.0)	
Total serum CK (IU/L)	4889.08±4705.23	753.2±558.6	0.08
<3 times ULN	0 (0.0)	2 (40.0)	0.01
3–10 times ULN	2 (22.2)	3 (60.0)	
>10 times ULN	7 (77.8)	0	
AST (IU/L)	140.33±65.2	300.80±326.7	0.34
ALT (IU/L)	77.6±47.7	128.7±142.7	0.33
Serum potassium (mmol/L)	4.1±0.5	2.6±0.6	0.001
ESR (mm in 1 h)	15.22±5.0	17.40±5.6	0.47
Electrophysiology			0.1
Abnormal NCS	0	2 (40.0)	1.0
Myopathic EMG	8 (88.9)	4 (80.0)	
Myopathic EMG with spontaneous activity	1 (11.1)	1 (20.0)	
Total hemoglobin (gm/dl)	13.9±1.9	12.3±2.5	0.21
PCV (%)	43.94±4.0	42.4±5.7	0.56
Platelet count (×10^3 cells/μl)	67.00±33.7	133.40±72.0	0.03
Thrombocytopenia (<150×10^3 cells/μl)	9 (100)	2 (40.0)	0.03
			OR=5.5 (1.6–19.3)
Total leukocyte count (cells/μl)	5678.89±2850.1	3662.00±593.5	0.07
Normal (4000–11,000)	6 (66.7)	1 (20.0)	0.09
Leukocytopenia (<4000)	2 (22.2)	4 (80.0)	
Leukocytosis (>11,000)	1 (11.1)	0	
Relative lymphocyte (%)	35.56±6.4	39.60±7.4	0.31
Relative lymphocytosis (>35%)	5 (55.6)	4 (80.0)	0.58

MRC = Medical Research Council, DRTs = Deep tendon reflexes, MBI = Modified Barthel index, PCV = Packed cell volume, CK = Creatine kinase, ULN = Upper limit of normal, AST = Aspartate aminotransferase, ALT = Alanine transaminase, ESR = Erythrocyte sedimentation rate, NCS = Nerve conduction studies, EMG = Electromyography, OR = Odds ratio

Spontaneous activity in EMG was seen in eight patients. Small amplitude, short duration polyphasic MUAP with early recruitment in myopathy occurs as a result of drop out of muscle fibers from the motor unit with no loss in total number of motor unit. Spontaneous activity in the form of fibrillation or positive sharp waves can occur in few causes of myopathy, especially in inflammatory causes with muscle membrane irritability. NCS is usually normal in myopathies except for reduced CMAP that can be seen with involvement of distal muscles. Any other abnormality in NCS suggests involvement of structures other than muscles. Spontaneous activity in myopathy suggests either inflammation or necrosis of the muscle.[10] Polymyositis, dermatomyositis, and myositis secondary to SLE are known to show spontaneous activity in

Table 4: Correlation of disability outcome parameters at 1 and 3 months with other variables in all thirty patients

Variable	MBI1		MBI3	
	r	*P*	*r*	*P*
Age (years)	0.21	0.26	−0.15	0.44
Duration of symptoms (days)	−0.63	0.001	−0.37	0.05
MRC sum score	0.13	0.50	0.40	0.03
MBI0	0.40	0.03	0.33	0.07
Total serum CK (IU/L)	−0.18	0.35	−0.42	0.2
Serum potassium (mmol/L)	−0.34	0.07	−0.24	0.20
AST (IU/L)	0	1.00	−0.40	0.03
ALT (IU/L)	−0.10	0.61	−0.42	0.02
ESR (mm in 1 h)	−0.46	0.01	−0.22	0.24
PCV (%)	−0.18	0.37	−0.15	0.94
Platelet count ($\times 10^3$ cells/μl)	−0.59	0.00	−0.34	0.06
Total leukocyte count (cells/μl)	−0.50	0.01	−0.08	0.66
Relative lymphocytosis (%)	0.58	0.00	0.37	0.04

MRC = Medical Research Council, CK = Creatine kinase, AST = Aspartate aminotransferase, ALT = Alanine transaminase, ESR = Erythrocyte sedimentation rate, PCV = Packed cell volume, MBI = Modified Barthel index

EMG. Two cases of dengue also showed spontaneous activity. Although spontaneous activity is not a commonly feature in muscle weakness secondary to dengue fever, some reports suggest that it can be present in some cases.[4,13,18]

Muscle biopsy was done in six cases which revealed polymyositis in one patient, dermatomyositis in one, nonspecific inflammatory myopathy due to SLE in one, nonspecific inflammatory myopathy in one, and normal in two patients of dengue. Polymyositis and dermatomyositis typically present with subacute symptoms of months but can present acutely also. In a study, muscle biopsy was done in 15 SLE patients with muscle symptoms and up to 50% of them showed myositis. Clinical evidence of myositis was present in 8.8% of SLE patients in registry.[19] Two patients of dengue fever who showed spontaneous activity underwent biopsy. Both of them had normal study. Studies of muscle biopsy in dengue myositis have revealed a range of findings from mild lymphocytic infiltrate, lipid accumulation, mitochondrial proliferation to foci of severe muscle damage in the form of hemorrhages and myonecrosis.[4,13,20] Histopathology in patients of hypokalemic paralysis due to dengue is lacking.[13]

Etiology was identified in 29 out of thirty cases. With 14 cases, dengue was the most common cause of acute myopathy in this study, followed by hypokalemia due to causes other than dengue in eight patients, pyomyositis in three, and one each of dermatomyositis, polymyositis, hyperthyroidism, and myopathy secondary to SLE. Cause in one case could not be identified. In patients with dengue, five had hypokalemia and nine had normokalemia. Viral myositis and electrolyte disturbance frequently manifest acutely as seen in earlier studies. Frequently reported cause of viral myositis is benign acute myositis due to influenza A or B seen more commonly in western population.[1,21,22] Many of them develop symptoms over hours today.[12,13,21,23-25] However, in recent years, neurological manifestations of dengue fever are frequently being identified and reported.[25,26] Acute myopathy due to dengue is one among them, which is one of the most common causes of acute myopathy due to infection and virus in areas where dengue is endemic. It is usually seen in rainy season when the dengue outbreaks occurred and reduced significantly as the mosquito breeding decrease with passing off of rainy season. The muscle involvement in dengue fever patients can be in the form of simple myalgia, myositis, hypokalemic paralysis, or rhabdomyolysis. In our study of 14 cases due to dengue, nine cases were of myositis and five due to hypokalemic paralysis. Hypokalemic weakness was seen in 13 cases, which included five cases due to dengue fever, three cases due to hypokalemic periodic paralysis, and one case each of renal tubular acidosis due to Sjogren's syndrome, renal tubular acidosis of unknown cause, acute pancreatitis, hyperthyroidism, and drug induced. These causes are similar to previous studies which studied etiologies in cases of hypokalemic paralysis.[12,14] Although the exact mechanisms as to why dengue causes hypokalemia are largely unknown, many postulated mechanisms are mentioned in literature. First, the presence of endothelial dysfunction occurring in dengue causes leakage of fluid and electrolytes from intravascular compartment. Second, renal tubular damage occurs in dengue fever which causes tubular loss of potassium. Third, stress due to dengue infection causes release of catecholamines and insulin, which leads to intracellular shift of potassium causing hypokalemia.[27] The causes also included two patients of hyperthyroidism, of which one patient had hypokalemia while the other had normokalemia. Both of them were also positive for anti-thyroid peroxidase antibody. The thyrotoxic periodic paralysis is one of the causes of hypokalemic paralysis. Increased sodium-potassium ATPase activity by thyroid hormone leads to rapid and massive shift of potassium intracellularly mainly muscles, hence leading to hypokalemia and weakness. When the hypokalemia is severe, it leads to structural muscle damage resulting in raised muscle enzymes. Graves' thyroid disease can also lead to muscle weakness of proximal predominant without hypokalemia associated with normal or hyperreflexia with normal CK level. The reason of weakness in this is increased basal metabolic rate, leading to depletion of energy stores resulting in easy fatigability and weakness. The weakness in Graves' disease is of longer duration compared to shorter episodic nature seen in thyroid hypokalemic periodic paralysis.[11,14] In our study, no cases of leptospirosis were seen though it remains important cause of myositis in certain endemic areas. Leptospirosis is endemic in five states (Gujarat, Maharashtra, Kerala, Tamil Nadu, Karnataka) and union territory of Andaman and Nicobar Islands.[28] Leptospirosis though not uncommon in Uttar Pradesh is relatively less common cause of febrile illness as compared to southern and western states of India. This might explain the absence of leptospirosis cases in our study. In our study, no cases had hypokalemic paralysis due to acute gastroenteritis. Although gastroenteritis is a well-known cause of hypokalemia, not much information is available about muscle paralysis due to hypokalemia, following gastroenteritis. In a report presented by Yurdakök *et al*., among 162 moderately dehydrated children caused by acute gastroenteritis, 15 (90%) were found to be hypokalemic (K^+<3 mEq/L). None of these patients had paralysis due to hypokalemia.[29] In another study by Kayal *et al*., out of 56 patients of hypokalemic paralysis, only two had acute gastroenteritis.[30] These studies might indicate that though hypokalemia is common in gastroenteritis, it is rarely severe enough to cause significant paralysis. In

addition, majority of patients of gastroenteritis who are critically ill are admitted in Medicine Unit of our hospital rather than neurology unit which might explain the absence of gastroenteritis cases in our study.

The baseline clinical severity parameters such as MSS and MBI0 failed to show any correlation with clinical, biochemical, hematological, or electrophysiological variables. However, the parameters of disability status at follow-ups such as MBI1 and MBI3 showed some notable correlations. Good outcome at 1 month correlated significantly with shorter duration of symptoms, better MBI0, lower serum potassium, lower ESR, lower platelet count and lower total leukocyte count, and higher relative lymphocyte percentage. While higher MSS at presentation, lower serum total CK level, thrombocytopenia, and relative lymphocyte percentage correlated with better outcome at 3 months. Since dengue (14 cases) and hypokalemia (seven cases other than due to dengue) constituted 70% of total patients and all these patients presented with <1 week duration of symptoms, the correlation study implies that these diseases have better prognosis compared to other causes of acute myopathy found in this study. These findings are in accordance with previous studies which showed excellent outcome in patients with dengue and hypokalemia with complete and rapid improvement after treatment.[4,12-14,24] Since thrombocytopenia, leukopenia, and relative lymphocytosis were commonly seen in those with dengue fever, these variables correlated with better outcome.

Of total thirty patients included in the study, 14 were of dengue fever. These patients were studied separately and compared to other 16 patients without dengue. Patients with dengue had significantly shorter mean duration of symptoms, more patients with fever and hyporeflexia, lower mean platelet count and total leukocyte count, higher mean relative lymphocyte percentage, more patients with thrombocytopenia and leukopenia, and more patients with relative lymphocytosis. Furthermore, though not statistically significant, dengue patients had more patients with skin lesions, more chances of patients presenting with both proximal and distal weakness, higher mean total CK level, lower ESR level, and higher mean total hemoglobin level. Hence, the presence of skin rashes, fever, and above-said impairments in hematological parameters, especially in hyperacute presentation (<1 week) of myopathy, one should suspect possibility of dengue fever more so in endemic areas. On comparing patient of dengue with hypokalemia with those of dengue myositis, hyporeflexia and leukopenia were more frequent in dengue with hypokalemia while serum CK >10 times and thrombocytopenia were seen more frequently in dengue myositis. The weakness in dengue with hypokalemia is mainly secondary to electrolyte imbalance and not due to structural damage hence the CK level is raised only marginally. In addition, there can be hyporeflexia and involvement of distal muscles with reduced CMAPs amplitude on NCS in dengue with hypokalemia. The inflammation and structural damage due to myositis lead to very high level of total serum CK level in dengue myositis and usually takes longer time (days compared to hours in dengue with hypokalemia) for symptoms to develop and also improve.[13]

Hence, the etiological spectrum in patients of acute myopathy can vary from metabolic, electrolyte, infectious to endocrine and inflammatory causes with varying clinical features, biochemical and hematological parameters, and outcome. There is no significant difference in electrophysiology parameters between various etiologies. EMG is more sensitive and NCS plays a role in ruling out other causes rather than ruling in myopathy. Biopsy may not be needed in majority of the patients as < 30% needed biopsy, of which only five proved to be decisive in making diagnosis (inflammatory myopathy in two, dermatomyositis in one, polymyositis in one and myopathy of unknown cause in one). Still diagnosis could be reached in all but one. Hence acute myopathy differs from chronic myopathies that one need to investigate for infections and electrolyte more than inflammatory, endocrine and other causes and relies less on biopsy for diagnosis. In addition, recovery is rapid and complete in majority which may not be the case in chronic myopathies.

Conclusion

Acute muscle dysfunction is caused by variety of causes including infectious and non infectious etiologies. The infectious causes differ in various parts of India in terms of micro-organism depending upon endemic zone. Hypokalemia associated with various disorders is commonest cause of acute muscle dysfunction. Dengue with hypokalemia is commonly associated with acute motor quadriparesis in North India. Electrodiagnostic studies ,though help in differentiating myopathy from neurogenic causes, do not determine etiological factors for acute myopathy. Histopathological assessment minimally helps in acute muscle dysfunction. The prognosis of acute muscle dysfunction is good if patients are treated early with diagnostic accuracy.

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Conflicts of interest
There are no conflicts of interest.

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