Assessment of Diaphragm Thickness by Ultrasonography in Guillain Barre Syndrome and Myasthenia Gravis

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Background:

The diaphragmatic thickening ratio measured by ultrasonography in neurological diseases remains unclear. Early prediction of diaphragmatic dysfunction may prevent the occurrence of respiratory complications in these cases. In this prospective observational cohort study, we compared the diaphragmatic thickening ratio in patients with Guillain Barre, Myasthenia gravis, and normal control. We predicted the occurrence of respiratory complications by using the ultrasound measurement of the thickening ratio of the diaphragm.

Methods: sixty subjects aged 18-65 years old of both sexes were allocated into three groups, each group contained 20 patients. The first one was the Guillain Barre syndrome group, the second was the myasthenic group, and the third was the control group. All the subjects of the study had no respiratory symptoms at the time of assessment. We measured the diaphragmatic thickness during inspiration and expiration for all subjects and then calculated the diaphragmatic thickening ratio. The patients of Guillain Barre were assessed clinically by MRC sum-score and Hughes score. Nerve conduction was done and CSF aspiration for all patients with Guillain Barre syndrome. The incidence of respiratory complications was calculated using the diaphragmatic thickening ratio to predict the occurrence of these complications.

Results: Data from sixty subjects (20 subjects in each group) were analyzed. The mean± SD of the diaphragmatic thickening ratio was (1.18 ±.12, 1.46 ±.4, 1.78 ±.23) and the p-value was <.001 on the right side. On the left side, the mean± SD was (1.19 ±.23, 1.3 ±.18, 1.67 ±.29) and the p-value was <.001. There was a significant difference between the thickening ratio in the Guillain Barre group more than in the other group.

Conclusion: the diaphragmatic thickness was significantly affected in patients with acute neuropathies and neuromuscular diseases. The ultrasound measurement of the diaphragmatic thickening ratio may be a good predictor of the occurrence of respiratory complications.

Keywords: Guillain Barre syndrome, Myasthenia Gravis, ultrasound, diaphragmatic thickening ratio.

DOI Number: 10.14704/nq.2022.20.9.NQ440126 **Neuro Quantology 2022; 20(9):1120-1128**

Introduction

Respiratory function may be affected by various types of neurological diseases, particularly acute neuropathies (Guillain Barre), and neuromuscular disorders (Myasthenia gravis), which are characterized by either illness of the respiratory muscles themselves or the nerve(s) supplying those muscles. (1) The patient may not be aware of his deteriorating respiratory condition and may not exhibit the normal expected clinical signs due to the limited activity brought on by the underlying neurological illness. Identifying people who are more likely to experience respiratory muscle weakness is crucial. (2)

There are numerous ways to examine the diaphragm's function. Transdiaphragmatic pressure (PDI) measurement is the gold standard for the diagnosis of bilateral diaphragmatic paralysis. This represents the difference in pressure between the abdomen and the esophagus during a maximal voluntary contraction. This procedure can only be used in a few clinics and laboratories due to its invasive nature. [3] Other noninvasive diagnostic methods for the assessment of respiratory dysfunctions including arterial blood gases, pulse oximetry, and pulmonary function testing are neither sensitive nor specific for detecting respiratory muscle weakness. [4]

Diaphragm paresis can be diagnosed with high sensitivity and accuracy using ultrasound. In addition to giving a non-invasive picture of the diaphragm muscle thickness, it is useful for electromyogram (EMG) studies since it may be used to direct needle insertion or to gauge the depth and location of the diaphragm, greatly lowering the risk of complications. [5] Recent studies suggest that ultrasound may be used to evaluate patients in intensive care units before they are extubated and determine whether diaphragmatic pacing may be beneficial. [6-8]

Diaphragmatic dysfunction-related respiratory symptoms are dependent on several variables, including unilateral or bilateral involvement, the underlying cause, the presence of other cardiopulmonary diseases, obesity, and previous diaphragmatic disease brought on by trauma, surgery, or neuromuscular disorders. When only one side of the diaphragm is affected, the patient may be asymptomatic or display symptoms of orthopnea or dyspnea on exertion, while the bilateral diaphragmatic affection typically exhibits dyspnea and orthopnea, which can happen while at rest. Patients typically exhibit cyanosis, bilateral reduction in breathing sounds, fast and shallow respiration, or paradoxical abdominal wall movement. [9]

It is difficult to predict how long it will take for functional recovery of the diaphragmatic dysfunction caused by neurological disorders. Partial or complete recovery may take months to years, and patients may still have ultrasound diaphragmatic affection even in the absence of any clinical respiratory symptoms. [10]

To our knowledge, Noda and their colleagues used ultrasound to assess diaphragmatic dysfunction in patients with neuromuscular disorders. [11] He measured the diaphragmatic thickness at resting end-expiration, while our study evaluated the diaphragmatic dysfunction in patients with neuromuscular diseases using the diaphragmatic thickening ratio that depends on diaphragmatic thickness at the end of maximal inspiration and thickness at the resting end- expiration.

Due to variations in inspiratory effort among individuals, the diaphragmatic thickening ratio has some limitations as it is evaluated at the end of maximal inspiration, resulting in significant measurement errors when applied to people with respiratory symptoms. [12] So, in our study, we measured the ratio in patients having no symptoms of respiratory affection and used it as a predictor of the occurrence of respiratory dysfunction.

We aimed in this study to compare the diaphragmatic thickening ratio in three groups, the first group was patients who presented with Guillain Barre syndrome and had no symptoms of respiratory affection, and the second group was controlled myasthenic patients who were free from respiratory symptoms and signs at the time of our study but had a previous history of respiratory affection and needed respiratory support more than a year ago, and the last group was normal peoples as a control. We hypothesized that Guillain Barre patients would have a greater impact on diaphragmatic thickness than the other two groups.

Patients and methods

The neurology department at Mansoura University Hospitals in Mansoura, Egypt, conducted this prospective observational cohort study from April 2022 to May 2022 on 60 patients who were allocated into three groups: the Guillain Barre group (GB), the Myasthenia Gravis group (MG), and the control group (C). There were 20 patients allocated to each group. A Clinical trial registry (NCT05324176) was acquired, and an Institutional Review Board (IRB) was obtained. Before enrolling any patients in this study, written informed consent was taken. Adult patients more than 18 years old of both sexes diagnosed with Guillain Barre syndrome or Myasthenia Gravis were included in this study. History of cardiopulmonary diseases, diaphragmatic disorders, body mass index of more than 30 kg/m^2, and respiratory dysfunction at the time of examination were excluded from the study.

Patients were admitted to the neurology department with clinical symptoms and an examination suggested GBS. Patients fulfilled the clinical diagnostic criteria and the diagnosis was confirmed. [13] To rule out GBS mimics, serum electrolytes, toxicological testing, and virology (HCV, HBV, and HIV) were performed, and history of preceding upper respiratory tract infection or diarrhea was taken. The time between the onset of weakness and admission was recorded. Patients with Myasthenia gravis who participated in the study had a history of one or more episodes of Myasthenic crisis that required respiratory support in the form of oxygen therapy or mechanical ventilation and a year or more has passed since the last crisis; however, at the time of the examination, the patients were controlled on their treatment and showed no signs of respiratory distress.

Guillain- Barre Patients underwent motor nerve conduction study of the median, ulnar, tibial, and peroneal nerves on both sides; assessments of F-M latencies, distal motor latency (DML), nerve conduction velocity (CV), and compound muscle action potential (CMAP) amplitude were also made. The median and ulnar nerves were each subjected to a sensory nerve conduction examination in a similar manner (DML is assessed), followed by classification of the patients into five groups: acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal (AMAN), acute motor sensory axonal (AMSAN), inexcitable, and equivocal. [14]

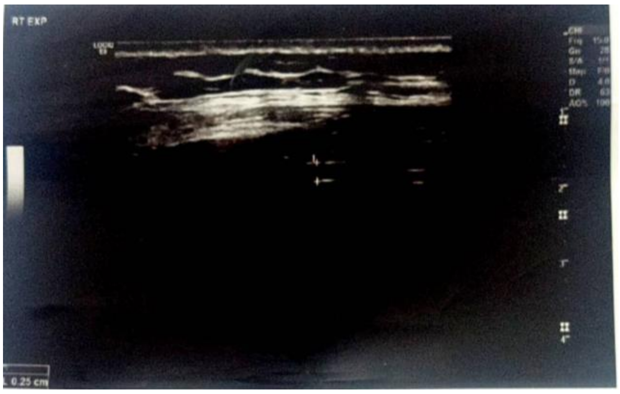
Respiratory rate and oxygen saturation (SPO_2), arterial blood gas, and pulmonary function tests were done to rule out any respiratory affection, then CSF aspiration for detection of the Cytoalbuminous dissociation

Clinical evaluation of Guillain Barre patients assessed by:

1-The Medical Research Council (MRC)grading for power: The MRC sum score is the sum of the MRC grades for the following muscle pairs: upper arm abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and ankle dorsiflexion (MRC grades range from 0-5). The MRC sum score is a number between 0 (complete paralysis) and 60 (normal strength), followed by allocation of the patient in one of three groups, group 1 (0 -36), group 2 (>36 - ≤48), and group 3 (>48 – 60) [15]

2-Hughes functional grading scale scores: The score scales from 0-6 (Grade 0 = normal; Grade 1 = mild signs or symptoms of neuropathy but able to perform the manual task; Grade 2 = able to walk without the assistance of a stick but not able to perform the manual task; Grade 3 = ability to walk with the aid of support, device, or stick; Grade 4 = bed or chair bound; Grade 5 = needing ventilatory support, and Grade 6 = dead). [16]

Technique for ultrasound assessment of diaphragmatic thickness: Near the zone of attachment, where the diaphragm touches the rib cage, both hemidiaphragm can be seen and this is defined as the zone of apposition. A 7–13 MHz linear array transducer of (Logiq E9, GE Healthcare, Milwaukee, Wisconsin, USA) was employed in a high-resolution ultrasound system. The probe should be angled perpendicular to the chest wall as per standard technique. It was positioned at the eighth or ninth intercostal space, spanning two ribs close to the anterior or mid-axillary line. The distinctive 3-layered structure, position beneath the intercostal muscles and subcutaneous tissue, and the extension deep to the ribs all served to identify the diaphragm as a three-layered structure with the hypoechoic (black) diaphragmatic muscle being enclosed between two parallel hyperechoic (bright) lines, the peritoneal fascia, and the diaphragmatic pleura. The center of the non-echogenic layer, which is thought to represent the fibrous layer in the center of the diaphragm, frequently displays a third hyperechoic line. The thickness was estimated directly from the frozen B-mode images The diaphragm will be hidden in more cephalad intercostal gaps by the highly hyperechoic lung shadow that enters the field of view during deep inspiration. After choosing the best intercostal space, the participant was told to breathe quietly while three pictures were taken at the end of a quiet expiration. The subject was then advised to take slow, deep breaths in and out, and three pictures were taken at the location of the thickest diaphragm, which the examiner could see (or at the point at which the diaphragm became obscured by the lung). The thickness of the diaphragm muscle was measured using electronic calipers at the area closest to the more caudal rib, where the two fascial lines encircling the muscle were parallel. The three images for each position were then averaged to provide a thickness at resting end expiration (T^{MIN}) and a thickness at maximal inspiration (T^{MAX}). A thickening ratio (TR) was then derived: T^{MAX}/T^{MIN}. [17] After the diaphragmatic assessment, the patients were managed according to the protocol of management of patients with Guillain Barre of our department and take the appropriate treatment and care. Patients were monitored for one month to detect the occurrence of any respiratory complication that was defined as dyspnea, tachypnea, orthopnea, hypoxia, need for oxygen support, and mechanical ventilation.



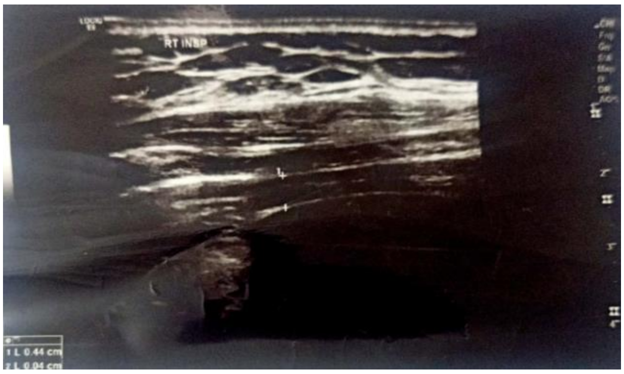


FIGURE 1. Ultrasound of the diaphragmatic images: In (A), at the resting end-expiration, the diaphragm is appeared as a dark structure (hypoechoic) between two bright (hyperechoic) fascial planes, in (B), the diaphragmatic thickness at the end of the deep inspiration.

We collected the baseline characteristics data for all subjects enrolled in the study (age, sex, weight, height, and body mass index (BMI)), and diaphragmatic thickness measurements:(T^{MAX}, T^{MIN}, TR)

From Guillain Barre patients, data were obtained about history of preceding URTI, or diarrhea, onset from weakness to admission, history of smoking, full examination, and presentation symptoms (sensory, motor, sensory&motor, bilateral facial, and bulbar affection). A nerve conduction study was done and then the patients were allocated to one of the five groups (AIDP, AMAN, AMSAN, inexcitable, equivocal). CSF aspiration and clinical evaluation by MRC sum score and Hughes were also done for them.

The primary outcome was the comparison of the diaphragmatic thickening ratio measurement in the three groups on both sides, while secondary outcomes were diaphragmatic thickness at the end of deep inspiration and at resting end-expiration on both sides in the three groups, the incidence of respiratory dysfunction in patients with Guillain Barre syndrome, the correlation between the MRC sub-score and the Hughes score with the diaphragmatic thickening ratio on both sides, the incidence of appearance of Cytoalbuminologic dissociation in CSF, and the incidence of each electrophysiological variant of patients with Guillain Barre.

The sample size was calculated by using the (G* power 3.1.9.4) program. Depending on the study done by Boon, et al, 2013. [17] The mean ± SD of the diaphragmatic thickening ratio (TR) was 1.8 ± .5, assuming $\alpha = .05$ and $\beta = .2$ (80% power) and conducting the one-way analysis of variance (ANOVA) test, 18 patients were needed in each group for decreasing TR by about 25%. Allowing for dropout cases, 20 patients were enrolled in each group.

statistical Analysis: The histogram and Kolmogorov-Smirnov test were used to determine whether continuous data were normal. Mean ± standard deviation, median (range), and number (percentage) represent normally distributed, nonnormally distributed, and categorical data, respectively. The normally distributed data were compared using one-way ANOVA with a post hoc LSD test, while non-normally distributed data were compared using the Kruskal-Wallis H test followed by Mann-Whitney U test if a significant difference between groups was present. Categorical data were compared using X^2. Correlation between the MRC sub-score and the Hughes score with the diaphragmatic thickening ratio was done by using the Spearman test. ROC curve was done to predict the occurrence of respiratory complications by using the diaphragmatic thickening ratio on both sides. IBM-SPSS statistical package was used for data analysis and a p value<0.05 was considered statistically significant.

Results:

The study contained 60 subjects allocated into three equal groups, each group had 20 subjects. We demonstrated patients baseline data in Table 1 and showed no significant difference between the three groups in age, sex, weight, height, and body mass index.

The diaphragmatic ultrasound measurements were presented in Table 1. The diaphragmatic thickness at the end of maximal inspiration (T^{max}) was greatly affected in patients with Guillain Barre syndrome more than in other groups on both sides, while the thickness at the resting end-expiration (T^{MIN}) showed no differences between the groups. The thickening ratio (TR) was highly affected in GBS patients more than in other groups on the right side, but the left side showed affection for Guillain Barre patients more than normal individuals, and no statistically significant difference between Guillain Barre and Myasthenic Patients.

The diaphragm is affected in the Myasthenia gravis group as regards the T^{MAX} on the right side only, and TR on both sides when compared with the normal individuals, but there was no difference between the two groups when measuring the T^{MIN}.

Our results showed that the patients with Guillain Barre presented with sensory manifestations in 2 patients (10%), motor manifestations in 6 patients (30%), and both sensory and motor symptoms in 11 patients (55%). Bilateral facial affection was presented in 5 patients (25%), while bulbar affection appeared in 3 patients (15%). Cytoalbuminologic dissociation appeared in 8 patients (40%), and respiratory complications occurred in 9 patients (45%). A nerve conduction study revealed that 10 patients (50%) were diagnosed as AIDP, 2 patients (10%) as AMAN, 2 patients (10%) as AMSAN, 2 (10%) patients as inexcitable, and 4 patients (20%) as equivocal.

Our Roc curve in figure 2 revealed that ultrasonographic measurement of diaphragmatic thickening ratio in predicting the occurrence of respiratory complications in patients with GBS had a cut-off point equal to or less than 1.1952 cm achieving 88.9% sensitivity and 63.6% specificity on the right side and a cut-off point equal to or less than 1.218 cm achieving 77.8% sensitivity and 72.7% specificity on the left side.

Table 2 compared the patients of Guillain Barre revealed respiratory complications with patients who did not show any respiratory dysfunction and demonstrated that the onset of weakness till admission was prolonged in patients with respiratory complications (3 (1-4) vs 1 (1-5)), and incidence of the presence of Cytoalbuminologic dissociation was greater in patients with respiratory complications.

There was a significant negative medium correlation between the Hughes score and the left TR (rho= .482, p value= .03), while a medium correlation and not significant between the MRC sum-score and the right TR (rho= -.408, p value= .07).

Table 1: patients' baseline data and diaphragmatic measurements in Guillain Barre patients, Myasthenic patients, and normal individuals.

	Guillain Barre (n=20)	Myasthenia (n=20)	Control (n-20)	P value
Age(years)	47.1 ±13.44	39.3 ±9.02	43.7 ±11.55	.1
Sex(M/F)	14/6	8/12	10/10	.2
Height(m)	1.8 ±.08	1.7 ±.07	1.7 ±.08	.2
Weight(kg)	75.2 ±4.64	76 ±6.57	72.9 ±3.71	.2
BMI(kg/m^2)	24.4 ±2.16	25.8 ±2.2	24.8 ±1.75	.09
Right T^{Max} (cm)	.25(.18-.64)	.35(.21-.43) ##	.43(.24-.6)	<.001*
Right T^{Min} (cm)	.21(.14-.49)	.23(.15-.37)	.22(.15-.35)	.5
Left T^{Max} (cm)	.25(.15-.6)	.3(.2-.44)	.34(.17-.54)	<.001*
Left T^{Min} (cm)	.19(.11-.48)	.23(.17-.32)	.22(.13-.31)	.2
Right TR	1.18 ±.12	1.46 ±.4 ##	1.78 ±.23	<.001*
Left TR	1.19 ±.23#	1.3 ±.18 ##	1.67 ±.29	<.001

Data are presented as mean±SD, median (range), and numbers.

Abbreviations: BMI; body mass index, T^{MAX}: diaphragmatic thickness at maximal inspiration, T^{MIN}: diaphragmatic thickness at resting end-expiration, TR: Thickening ratio.

*significance difference between the Guillain Barre group and the other groups.

significance difference between the Guillain Barre group and the control group.

significance difference between the Myasthenia Gravis group and the control group.

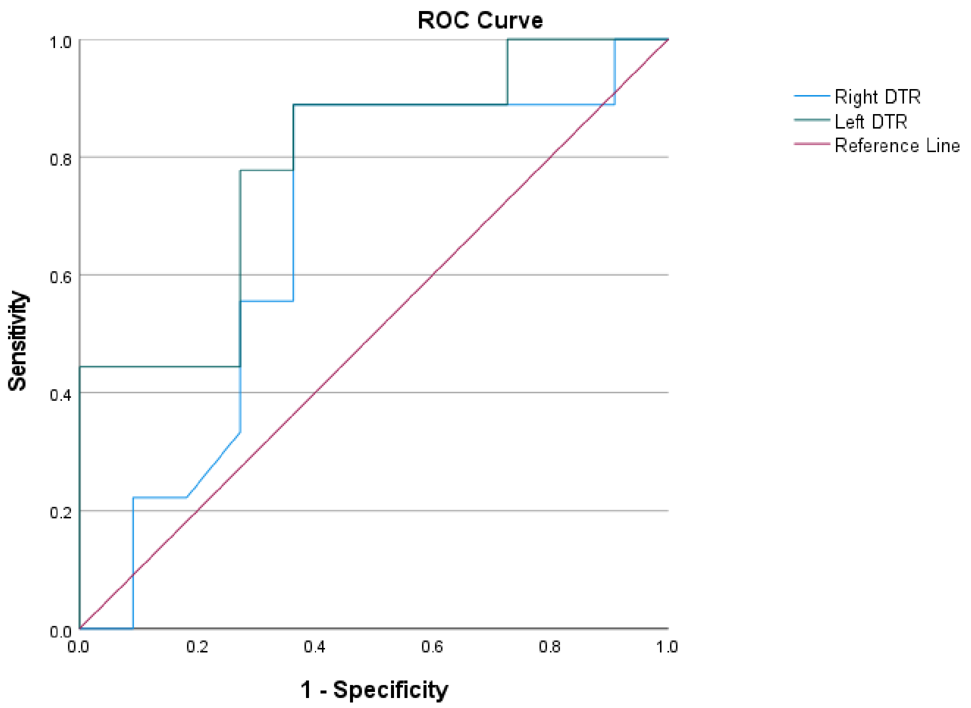


Figure 2: ROC curve for ultrasound measuring of diaphragmatic thickening ratio on both sides in predicting the occurrence of respiratory complications.

Table 2: Preceding events, clinical presentations, electrophysiological variants, and CSF analysis in Guillain Barre patients revealed respiratory dysfunction or not.

	Normal (n=11)	Abnormal (n=9)	P value
Onset from weakness to admission (days)	3 (1-4)	1 (1-5)	.03*
Preceding events			
URTI (Y/N)	3/8	5/4	.2
Diarrhea	4/7	2/7	.5
Smocking (Y/N)	3/8	3/6	.8
Clinical presentation			.7
NO Sensory&Motor	1	0	
Sensory	1	1	
Motor	4	2	
Sensory&Motor	5	6	

Bilateral facial weakness (Y/N)	4/7	1/8	.2
Bulbar symptoms (Y/N)	2/9	1/8	.7
Electrophysiological subtypes			.5
AIDP	6	4	
AMAN	1	1	
AMSAN	0	2	
Inexcitable	1	1	
Equivocal	3	1	
CSF Cytoalbuminologic dissociation (Y/N)	2/9	6/3	.03*

Data are presented as median (range), and numbers.

Abbreviations: URTI; upper respiratory tract infection, AIDP; acute inflammatory demyelinating polyneuropathy, AMAN; acute motor axonal, AMSAN; acute motor sensory axonal.

*significance difference between the two groups.

Discussion

One of the most frequent causes of neuromuscular respiratory failure is Guillain-Barre syndrome (GBS), which results in 17%–30% of patients needing mechanical ventilation. In individuals with GBS, respiratory failure is a major cause of morbidity and mortality and is associated with poor outcomes. [18] The inspiratory and expiratory muscles of the respiratory system gradually weaken because of GBS. According to theory, demyelination of the phrenic nerve is what causes the diaphragm to weaken. The early manifestations of respiratory failure are limited to tachypnea, tachycardia, air hunger, broken sentences, and the inability to speak whole sentences without pause. later signs of respiratory failure include the use of accessory respiratory muscles, paradoxical breathing, and orthopnea, which point to severe diaphragmatic weakness. [19]

Our study demonstrated that the diaphragmatic thickening ratio (TR) and thickness at maximal inspiration (T^{MAX}) were more affected in patients with Guillain Barre syndrome than in controlled Myasthenic patients and normal individuals, while the diaphragmatic thickness at the resting end expiration (T^{MIN}) showed no statistical difference between the three groups.

Analysis of our Roc curve revealed that ultrasonographic measurement of diaphragmatic thickening ratio in predicting the occurrence of respiratory complications in patients with GBS had a cut-off point equal to or less than 1.1952 cm achieving 88.9% sensitivity and 63.6% specificity on the right side and a cut-off point equal to or less than 1.218 cm achieving 77.8% sensitivity and 72.7% specificity on the left side.

In our study, T^{MAX} results showed a significant reduction, because it was measured at the end of maximum inspiration that required a full expansion of the thoracic cavity, to take a full vital capacity, which is not present in GBS patients, besides limited diaphragmatic contraction caused by phrenic nerve demyelination, which is in the line with studies that showed the affection of the vital capacity in patients with GBS. While we measured T^{MIN} during resting end-expiration and it was not mainly affected as it was measured in patients who had no symptoms or signs of respiratory dysfunction besides measuring at resting end-expiration and not forced expiration.

Also, the thickening ratio had good sensitivity and specificity in predicting and confirming diagnosis accuracy of respiratory dysfunction. Several studies demonstrated multiple risk factors as predictors of respiratory dysfunction in patients with GBS including days between the onset of weakness and admission, MRC sum score, presence of facial, and/or bulbar weakness, rapid progressive motor weakness, areflexia, descending weakness, dysautonomia, and electromyographic features of nerve conduction block. [20,21] Most of these risk factors are leading to or associated with the affection of the inspiratory and expiratory muscles or the affection of the nerves that are supplying these muscles. [22] However, our study was the first to directly measure the diaphragmatic thickness ratio as a predictor of respiratory complications in neuromuscular disorders. The hypothesis of our study comes from the pathophysiology of respiratory insufficiency in patients with GBS that results from the affection of the phrenic nerve followed by diaphragmatic affection.

Several studies have addressed one of the most important questions regarding the acute affection of the diaphragm in Guillain-Barré patients and demonstrated rapid affection of the diaphragm after a brief period. One such study was conducted by López Escárraga and colleagues, who measured the diaphragmatic thickening ratio 20 minutes after the interscalene block and discovered that it was severely affected due to phrenic nerve blockade at the site of the block. [23] Another study was done by Cavayas and their colleagues and found that patients who started cardiac surgery with low diaphragmatic thickness were prone to postoperative pulmonary complications more than other patients who started with normal diaphragmatic thickness and these complications appeared rapidly postoperative in the form of pneumonia, need for mechanical ventilation postoperative, or lung collapse. [24]

Despite being under control and showing no signs of respiratory impairment, the myasthenic patients in our study had a smaller diaphragmatic thickening ratio than normal individuals and a greater diaphragmatic thickening ratio than patients with acute neuropathy. Our explanation for this diaphragmatic affection, in chronic neuromuscular patients who did not show respiratory affection symptoms and were maintained on controlled treatment, is due to wasting and atrophy of the diaphragm muscle tissue to a degree that does not affect the diaphragm's ability to be fully expanded and take a full vital capacity in a deep breath. However, when the diaphragmatic capacity is affected and the disease pathology is activated, these patients are vulnerable to severe respiratory dysfunction.

Spontaneous recovery of the diaphragm is differed according to the cause of injury, iatrogenic injury mainly takes a short time to recover in comparison to pathological causes, and the mean time for recovery in the study done by Summerhill was 14.9 +- 6.1 months. Seven of the 11 patients who recovered did not show US signs of recovery until more than 1 year had passed. This is coping with our finding as myasthenic patients showed diaphragm affection by the US, despite having no respiratory symptoms. [10]

Some limitations were present in this study, firstly, the smallest size, however, we calculated the sample size, and the effect size was relatively large. Secondly, this study was designed as a preliminary study to explore the ultrasound measurements of the diaphragmatic thickness in different neurological disorders and not cover all the points that made the subjects enrolled in the study matched, for example, the onset from the appearance of the weakness to admission in Guillain Barre patients was not fixed, so the time of ultrasound examinations was not fixed in all cases. Myasthenic patients must not have respiratory symptoms at the time of examination and had at least one crisis that needed respiratory support at least one year ago, but also the time of examination was not fixed in all cases. The number of crisis attacks and the need for mechanical ventilation or not was not included. Another limitation was the time of CSF aspiration which could be normal if examined early in the disease and finally not classify the respiratory complications and detected the incidence of the patients needing oxygen support, non-invasive ventilation, and mechanical ventilation.

In conclusion, the diaphragmatic thickening ratio was decreased in patients with Guillain Barre more than in controlled Myasthenic patients and normal individuals. The diaphragmatic thickening ratio measurements were a good predictor in detecting the occurrence of respiratory complications. Finally, the onset from the appearance of the weakness till admission, and the presence of Cytoalbuminologic dissociation were correlated with the occurrence of the respiratory complications.

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