

A case report on the use of processed *Glycyrrhiza uralensis* extract and Korean medical treatment for a patient with Amyotrophic Lateral Sclerosis(ALS)*

Eun Hye Cha^{1,2}, Seong Jin Lee^{1,2}, Ji In Lee^{1,2}, In Ja Song³ and Sung Chul Kim^{1,2,*}

¹Department of Acupuncture & Moxibustion Medicine, Wonkwang University Gwangju Korean Medical Hospital

²Nervous & Muscular System Disease Clinical Research Center of Wonkwang University Gwangju Korean Medical Hospital

³Department of Nursing, Gwang-Ju Womens University



[Abstract]

Objectives : The serum creatine kinase(CK) level of Amyotrophic Lateral Sclerosis(ALS) patients suggests that it may be an independent prognostic factor for the survival of ALS. We report the changes of serum CK level of ALS patients treated by administering processed *Glycyrrhiza uralensis* extracts and Korean medical treatments.

Methods : We provided an ALS patient with processed *Glycyrrhiza uralensis* extracts and Korean medical treatments including acupuncture, pharmacopuncture and herbal medicine. The serum CK level was checked every month. The changes of ALSFRS-R and MRC grade were checked every month for additional result.

Results : The serum CK level as the prognostic factor for the survival of ALS gradually decreased for three months. However, ALSFRS-R decreased by two points at the second trial. MRC rate had no change for three months.

Conclusion : Combined administration of processed *Glycyrrhiza uralensis* extracts and Korean medical treatment could be meaningful possibilities in the treatment of ALS. We should conduct further studies to solve the limitations of this case study.

Key words :

Amyotrophic lateral sclerosis;
Glycyrrhiza uralensis;
 Creatine kinase;
 Korean medical treatment

Received : 2016. 05. 11.
 Revised : 2016. 05. 29.
 Accepted : 2016. 06. 03.
 On-line : 2016. 06. 20.

※ This study was supported by the Traditional Korean Medicine R&D Program funded by the Ministry of Health & Welfare through the Korea Health Industry Development Institute(KHIDI) (HI11C2142).

* Corresponding author : Department of Acupuncture & Moxibustion Medicine, Wonkwang Gwangju Oriental Medical Hospital, 543-8, Juwol-Dong, Nam-gu, Gwangju, Republic of Korea
 Tel : +82-62-670-6441 E-mail : kscndi@hanmail.net

I. Introduction

Amyotrophic lateral sclerosis(ALS) is a neurological disease of unknown origin characterized by selective degeneration and death of upper and lower motor neurons. It almost invariably progresses to paralysis and death over a 1~5 year time course. At present, there is no therapy that can reverse loss of functions¹⁾.

Until now, Riluzole remains the only medication with demonstrated efficacy and regulatory approval for the treatment of ALS. Although it is not a cure, research has shown that it can prolong survival for 2~3 months²⁾. In addition, riluzole has no effects on rates of changes in functional capacity, muscle strength, respiratory function, or quality of life³⁾. Thus, the development of novel drugs to treat ALS will be required.

Glycyrrhiza uralensis is a perennial legume containing 6~14 % glycyrrhizin components with a sweet flavor. It has been mostly used as a constituent of oriental medicine, so the safety of its use has already been proven. The key component of *Glycyrrhiza uralensis* contains glycyrrhizin, glycyrrhetic acid, liquiritin, and isoliquiritin, and it is used for medicinal effects such as of relieving pain, suppressing spasm, preventing cough, and loosening phlegm. It is widely known that *Glycyrrhiza uralensis* has pharmacological action such as anti-inflammatory action, a acting analgesic and anti-bacterial effect, etc⁴⁾.

The diagnosis of ALS is mostly taken with clinical methods, so there is no diagnostic test or biomarker for this condition. The CK levels of some ALS patients may be elevated moderately. It is reported that 23~75 % of ALS patients experienced CK elevation⁵⁾.

Therefore, we provided a hospitalized ALS patient with processed *Glycyrrhiza uralensis* extract and Korean medical treatments such as acupuncture, pharmacopuncture and herbal medicine. The serum CK level was checked for a key indicator. The changes of ALSFRS-R and MRC grade

were also checked every month for additional indices. We reported the changes that appeared to ALS patient during hospitalized period.

II. Case study

1. Patient

Im ○ ○, Man, 43 years
(Height : 174 cm, Weight : 73 kg)

2. Symptoms

Limb weakness, dysarthria, and fasciculation

3. Onset

2013.

4. Past medical history

N/S

5. Family history

N/S

6. Present medication

Individual antihypertensive drug. 1 T # 1

7. Present history

- 1) 2013, Lt. hand weakness onset
- 2) 2013, Winter Rt, leg weakness developed

- 3) 2014. 11. Lt. leg tremor developed, C-spine MRI, EMG etc. 'Motor neuron disease' diagnosed.
- 4) 2015.3 Visiting Gwang-Ju Oriental Medical Hospital, Wonkwang University and had taken acupuncture treatment several times.
- 5) 2016. 1.4~2016.4.4
Gwang-ju Oriental Medical Hospital of Wonkwang University, received admission treatment

8. Examination views

- 1) ECG : Minimally abnormal or normal variation
ECG
- 2) Neurological examination
Mental sate : Alert
pupil reflex : 2+ /2+
Biceps reflex : → →
Babinski sign : - -
Dysarthria grade : 1

9. Korean medical diagnosis

Wei symptom(痿證)

10. Treatment method

1) Processed *Glycyrrhiza uralensis* extract

Processed *Glycyrrhiza uralensis* extract (Gamcho extract powder Hanpoong) 4.32 g manufactured by

Table 1. Processed *Glycyrrhiza uralensis* extract administration

Date	2016.1.4- 2016.2.11	2016.2.12- 2016.2.18	2016.2.19- 2016.4.22
Dose	4.32 g/d	ceased	4.32 g/d

Hanpoong Co., Ltd. was applied from 2016.1.4 to 2016.4.22. (Not applied during 2016.2.12.-2016.2.18.) Processed *Glycyrrhiza uralensis* extract was administered to the patient 30 minutes after lunch (Table 1).

2) Acupuncture & Pharmacopuncture

(1) Acupuncture

Hua-Tuo-Jia-Ji-Xue acupuncture treatment was conducted by single-use 0.3 × 40 mm needles (DongBang acupuncture Inc, Korea) for 15 minutes. Bulbar palsy treatment was conducted by stimulating the soft palate and applying acupuncture in Geumjin Okaek acupoints by single-use 0.4 × 0.75 mm needles (DongBang acupuncture Inc, Korea).

(2) Pharmacopuncture

After checking for allergic reactions to a skin test, 0.1 cc of bee-venom pharmacopuncture (Jaseng pharmacopuncture institute, BV2) was administered equally on the acupoints of Hapgok (LI04) · Gokji(LI11) · Joksamni(ST36) · Taechung(LR03).

0.1 cc of *Hominis placenta* pharmacoacupuncture(Jaseng pharmacopuncture institute, C1-JH) was administered on the acupoints of Jungwan (CV04) · Gwanwon(CV12)

Table 2. Herbal Medicine Treatment

Date	Herbal medicine
2016.1.4~2.10	<i>Curcuma longa</i> 6 g, <i>Salvia miltiorrhiza</i> 6 g, <i>Gastrodia elata</i> 8 g, <i>Chaenomeles sinensis</i> 6 g, <i>Polygala tenuifolia</i> 6 g, <i>Paeonia japonica</i> 6 g, <i>Atractylodes japonicam</i> 6 g and processed <i>Aconitum carmichaeli</i> (manufactured by Hanpoong Co., Ltd. Aconibal Tab.)
2016.2.17.~3.1	<i>Panax ginseng</i> 10 g, <i>Astragalus membranaceus</i> 10 g, <i>Salvia miltiorrhiza</i> 15 g, <i>Chaenomeles sinensis</i> 4 g, <i>Crataegus pinnatifida</i> 4 g, <i>Amomum cadamomum</i> Linné 4 g, <i>Amomum villosum</i> 4 g, <i>Atractylodes japonica</i> 8 g
2016.3.4~4.22	<i>Curcuma longa</i> 6 g, <i>Salvia miltiorrhiza</i> 6 g, <i>Gastrodia elata</i> 8 g, <i>Chaenomeles sinensis</i> 6 g, <i>Polygala tenuifolia</i> 6 g, <i>Paeonia japonica</i> 6 g, <i>Atractylodes japonicam</i> 6 g and processed <i>Aconitum carmichaeli</i> (manufactured by Hanpoong Co., Ltd. Aconibal Tab.)

Table 3. Changes of serum creatine kinase level

Date	Creatine Kinase level (reference value : 24-195)
2016.1.4	250.0H
2016.2.13	242.0H
2016.3.14	212.0H

3) Herbal medicine

2016.1.4~2016.2.10 Prescription named ‘加味芍藥甘草附子湯’ was administered three times a day 30 minutes after each meal.

2016.2.17~2016.3.1 Another prescription was administered three times a day 30 minutes after each meal due to general weakness.

2016.3.4~2016.4.22 Prescription named ‘加味芍藥甘草附子湯’ was administered three times a day 30 minutes after each meal.

11. Assessment & Result

It was the changes of serum Creatine Kinase level that was a primary result.

Serum creatine kinase level was checked every month (Table 3). The serum CK level was gradually decreased for three months.

Secondary result was changes of ALSFRS-R. ALSFRS-R score was also checked every month (Table 4, 5). In this case, ALSFRS-R was two points

Table 4. Changes of ALSFRS-R score

	2016.1.5	2016.2.15	2016.3.15
Speech	3	3	3
Salivation	4	4	4
Swallowing	4	4	4
Handwriting	3	2	2
Cutting food and Handling utensils (patients without gastrostomy-feeding tube)	3	2	2
Dressing and Hygiene	3	3	3
Turning in Bed and Adjusting Bed Clothes	2	2	2
Walking	2	2	2
Climbing Stairs	1	1	1
Dyspnea	4	4	4
Orthopnea	4	4	4
Respiratory insufficiency	4	4	4
K-ALSFRS-R Score	37	35	35

decreased in the second time period. The score measured in the second time was the same as the one in the third time.

Additional result was changes of MRC grade (Table 5). The score of MRC rate was no change.

Table 5. Changes of MRC grade

	2016.1.4		2016.2.15		2016.3.15	
	right	left	right	left	right	left
shoulder	4+	4+	4+	4+	4+	4+
elbow	4+	4+	4+	4+	4+	4+
wrist	4	4	4	4	4	4
finger	4+	4+	4+	4+	4+	4+
hip	4+	4+	4+	4+	4+	4+
knee	4+	4+	4+	4+	4+	4+
ankle	4+	4+	4+	4+	4+	4+
1 st toe	4+	4+	4+	4+	4+	4+

III. Discussion

Amyotrophic lateral sclerosis(ALS) is a neurodegenerative disease characterized by dominant involvement of upper and lower motor neurons, leading to progressive weakness of bulbar, limb, thoracic and abdominal muscles. Within 2–4 years, it causes progressive and severe muscle weakness, eventually causing death due to respiratory muscle palsy^{6,7}. No curative treatment is available; therefore, the mainstay of management is primarily supportive and symptomatic⁸.

It has been demonstrated that *Glycyrrhiza uralensis* has antiviral, antimicrobial, anti-inflammatory, hepatoprotective, and blood pressure-increasing effects *in vitro* and *in vivo*. Additionally, *Glycyrrhiza uralensis* may be effective in treating hyperlipidaemia and inflammation-induced skin hyperpigmentation. The antiulcer, laxative, antidiabetic, anti-inflammatory, immunomodulatory, antitumour and expectorant properties of *Glycyrrhiza uralensis* have been investigated. Also, *Glycyrrhiza uralensis* may also be useful in preventing neurodegenerative disorders⁹. So, it could be a possible substance for treating neural disease such as ALS. Glycyrrhizic acid is the major and bioactive substance of *Glycyrrhiza uralensis*. Glycyrrhizic acid is neuroprotective in the post-ischemic brain mainly through anti-excitotoxic and anti-oxidative effects. Recently, it was reported that Glycyrrhizic acid protects DPC12 cells against glutamate-induced neurotoxicity mainly through ERK and mitochondria-related pathways¹⁰. It is considered to be very important because the pathology of ALS is related to glutamate. Glutamate-induced excitotoxicity has lain at the core of theories behind the pathological mechanism of neurodegenerative disease, including mitochondrial dysfunction, oxidative stress, and protein aggregation, that lead to neurodegenerative cell death. Riluzole, which possesses anti-glutamatergic properties, is approved as neuroprotective for ALS¹¹. However, high intake of *Glycyrrhiza uralensis*

can cause hypermineralocorticoidism with sodium retention and potassium loss, edema, muscle weakness, increased blood pressure and depression of renin-angiotensin-aldosterone system¹². The severity of symptoms depends on the dose and duration of licorice intake, as well as the individual susceptibility¹³. So, on this study, we checked a blood test every month to prevent the side-effects mentioned above.

Hua-Tuo-Jia-Ji-Xue(華佗夾脊穴) is located in about 0.5 Cun(寸) at both side of spinous process of each cervical, thoracic, lumbar and sacral vertebra. It has a therapeutic effect for musculoskeletal diseases, and nervous system diseases¹⁴. Based on this, Hua-Tuo-Jia-Ji-Xue was selected to treat the above ALS patient.

Bee-venom, and *hominis placenta* pharmacopuncture were used for relieving pain caused by joint contracture, treating muscle weakness, and strengthening the immune system. Lee et al. reported that pretreatment of neuronal and microglial cells with bee-venom significantly inhibited glutamate-mediated toxicity. Therefore, bee-venom treatment could be useful for neurodegenerative diseases such as ALS or motor neuron disease¹⁵. Also, it is reported that *hominis placenta* could be a potential treatment strategy in neurodegenerative diseases. *Hominis placenta* significantly prevented cell loss and protected neurites against MPP+ toxicity¹⁶.

Gami-Jakyak Gamcho buja Decoction(加味芍藥甘草附子湯) was administered above patient. Gami-Jakyak Gamcho buja Decoction was developed for treating amyotrophic lateral sclerosis patients with pain, joint contracture and muscular weakness. Jakyak-gamcho decoction has been used in traditional medicine to relieve pain, muscle spasms and cold syndrome due to blood deficiency¹⁷.

An elevated serum CK is considered as a marker of muscle damage. An obvious explanation of raised CK in ALS is muscle atrophy resulting from degeneration of motor neurons. The CK levels may then reflect severity of the underlying disease process and extent of muscle denervation, in which

case a higher level may be associated with a worse prognosis¹⁸.

The Amyotrophic Lateral Sclerosis Functional Rating Scale(ALSFRS) and the revised version that includes respiratory function(ALSFRS-R) is the most widely used instrument to measure function in ALS clinical trials¹⁹.

When clinical progress of neuron motor disease is evaluated, it's quite important to precisely measure muscular strength. The Manual Muscle Test of Medical Research Council (MRC) is traditionally and widely used to evaluate muscular strength because of strong points of its simplicity and credibility²⁰.

In this case study, the CK level of the ALS patient was measured every month, three times in total (for 3 months) and was gradually decreased. Even though it didn't reach normal figure and there is a limit that the CK level may not be an index that directly shows a progression of disease, the result of gradual decrease of CK level was shown. This means that muscle damage rate was gradually decreased for three months.

ALSFRS-R was used as additional indices (the total number of points is 48). When the score was measured in the second time, two points decreased. The score measured in the second time was the same as the one in the third time. This means that the patient's condition was aggravated 2016.1.5 to 2016.2.15. However, through the periods of 2016.2.15 to 2016.3.16, the patient's condition was preserved. It seems that due to disorder of liver function, the patient's condition was worsening temporarily. MRC scale was also used as another used as additional indices. Each score measured three times had no change. This means that muscular strength of this patient was maintained stable for three months.

During hospitalization periods, the patient had general weakness and liver somatic index slightly increased on February 13, 2016, so all the medication had ceased for the periods of 2016.2.11~2016.2.16 while only acupuncture treatment and pharmacopuncture were applied. When the pa-

Table 6. Changes of liver function test

	AST(12-33)	ALT(5-35)	ALP(96-254)
2016.1.4	22.0	25.0	153.0
2016.2.13	27.0	46.0	136.0
2016.3.14	20.0	32.0	119.0

tient's condition improved and liver somatic index didn't increase, the medication began again from February 17, 2016.

As mentioned before, high intake of *Glycyrrhiza uralensis* and long-term administration can cause side effects such as hypocalcemia and increased blood pressure. In this case study, potassium level and blood pressure remained stable. But liver somatic index temporarily increased. When liver somatic index was measured after administration of *Glycyrrhiza uralensis*, liver somatic index no longer increased(Table 6). Therefore, it appears that the increase of liver somatic index is irrelevant to administration of *Glycyrrhiza uralensis*.

In this study, although ALSFRS-R was decreased two points, the serum CK level as the key indicator was gradually decreased. Furthermore, the MRC rate was retained stable. Therefore, we suspect that our findings could open up new clinical guideline possibilities.

However, this study has its limitations on one case and setting control group as well as many kinds of oriental medication were applied at the same time, so it's not clear which treatment is more effective among them. Moreover, even though CK level, ALSFRS-R, and MRC scale were set as a key indicator to catch up with progress, it has its limitation that they would not be figures which can objectively apprehend the progress.

As ALS is a rare incurable disease, a supportive and symptomatic treatment has been normally carried out until now. Because this study has an example with one patient, it's hard to discuss significance about the effect of combined administration of *Glycyrrhiza uralensis* and Korean medication treatment at the same time. However, as long as we steadily continue to conduct more

studies to yield concrete evidence, it is surely believed that these researches help improvement of symptoms and life-extension for patients.

IV. References

1. C.Carlesi, L. pasquali, S. piazza et al. Strategies for clinical approach of neurodegeneration in amyotrophic lateral sclerosis. Archives italiennes de biologie. 2011 ; 149(1) : 151.
2. Richard W. Orell. Motor neuron disease : systematic reviews of treatment for ALS and SMA. British Medical Bulletin. 2010 ; 93(1) : 145-6.
3. Lacomplex L, Bensimon G, Leigh PN et al. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study group II. Lancet. 1996 ; 347(9013) : 1425-31.
4. Yoon MY, Jun KI, Son ES et al. Induction of Glutathione S-transferase Activity by the Extracts of *Glycyrrhiza uralensis* Fischer. Appl Biol Chem J. 2008 ; 51(3) : 228-9.
5. Gibson SB, Kasarskis EJ, Hu N et al. Relationship of creatine kinase to body composition, disease state, and longevity in ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2015 ; 16(7-8) : 473-7.
6. Ince PG, Lowe J, Shaw PJ. Amyotrophic lateral sclerosis : Current issues in classification, pathogenesis and molecular pathology. Neuropathol Appl Neurobiol. 1998 ; 24(2) : 104-17.
7. Andersen PM, Abrahams S, Borasio GD et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)-revised report of an EFNS task force. Eur J Neurol. 2012 ; 19(3) : 360.
8. Bae JS, Hong YH, Baek W et al. Current status of the diagnosis and management of amyotrophic lateral sclerosis in Korea : A multi-center cross-sectional study. J Clinical Neurol. 2012 ; 8(4) : 293-300.
9. Data of Electronic Media Morse SS. Wikipedia. Licorice. Available from : URL : <https://en.wikipedia.org/wiki/Licorice>.
10. D. Wang, T.Q. Guo, Z.Y. Wang et al. ERKs and mitochondria-related pathways are essential for glycyrrhizic acid-mediated neuroprotection against glutamate-induced toxicity in differentiated PC12 cells. Braz J Med Biol Res. 2014 ; 47(9) : 777-8.
11. Blasco H, Mavel S, Corcia P, Gordon PH. The glutamate hypothesis in ALS : pathophysiology and drug development. Curr Med Chem. 2014 ; 21(31) : 3551.
12. Jo SG, Im BG, Jo HG et al. Licorice induced hypokalemia. Kidney research and clinical practice. 2001 ; 20(6) : 1021-5.
13. Park KA, Seok SJ, Kim SJ et al. A Case of licorice-Induced hypokalemic rhabdomyolysis in a patient using a diuretic drug. Korean J Med. 2011 ; 80(2) : 258.
14. Ahn SG, Lee SR, Yang YS. The treatise research on Hua-Tuo-Jia-Ji-Xue. The Acupuncture. 2000 ; 17(4) : 139.
15. Lee SM, Yang EJ, Choi SM et al. Effects of Bee Venom on Glutamate-Induced Toxicity in Neuronal and Glial Cells. Evid Based Complement Alternat Med. 2012 ; 2012 : 368196.
16. Jeon HJ, Nam SS, Kim YS. Neuroprotection of Dopaminergic Neurons by Hominis placenta Herbal Acupuncture in in vitro and in vivo Models of Parkinson's Disease Induced by MPP+/MPTP Toxicity. The Acupuncture. 2015 ; 32(1) : 23-36.
17. Guo L, Cho SY, Kang SS et al. Orthogonal array design for optimizing extraction efficiency of active constituents from jakyakgamcho decoction, the complex formula of herbal medicines, paeoniae radix and glycyrrhizae radix. J Ethnopharmacol. 2007 ; 113(2) : 306-11.
18. M. K. Rafiq, E. Lee, M. Bradburnb. et al. Creatine kinase enzyme level correlates positively with serum creatinine and lean body mass, and is a prognostic factor for survival in amy-

- otrophic lateral sclerosis. *Eur J Neurol*. 2016 ; 23(6) : 1071-8.
19. Cedarbaum JM, Stambler N, Malta E et al. The ALSFRS-R : a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). *J Neurol Sci*. 1999 ; 169(1-2) : 13-21.
20. Kim SC, Na WM, Lim NR et al. A pilot clinical study on the Traditional Korean Medicine treatment of Amyotrophic lateral sclerosis. *J pharmacopuncture*. 2009 ; 12(1) : 59.

Appendix.

1. ALSFRS-R

1. Speech
 - 4) Normal speech processes.
 - 3) Detectable speech disturbances.
 - 2) Intelligible with reepeating.
 - 1) Speech combined with nonvocal communications.
 - 0) Loss of useful pseech.
2. Salivation
 - 4) Normal.
 - 3) Slight but definite excess of saliva in mouth ; may have nighttime drooling.
 - 2) Moderately excessive saliva ; may have minimal drooling
 - 1) Marked excess of saliva with some drooling.
 - 0) Marked drooling ; requires constant tissue or handkerchief.
3. Swallowing
 - 4) Nromal eating habits.
 - 3) Early eating problems ; occasional choking.
 - 2) Dietary consistency changes.
 - 1) Needs supplemental tube feeding.
 - 0) Nothing by mouth(NPO) ; exclusively parenteral or enteral feeding.
4. Handwriting
 - 4) Normal.
 - 3) Slow or sloppy ; all words are legible.
 - 2) Not all words are legible.
 - 1) Able to grip pen but unable to write.
 - 0) Unable to grip pen.
5. Cutting Food and Handling Utensils(patients without gastrostomy-feeding tube)
 - 4) Normal.
 - 3) Somewhat slow and clumsy, but no help needed.
 - 2) Can cut most foods, although clumsy and slow ; some help needed.
 - 1) Food must be cut by someone, but can still feed slowly.
 - 0) Needs to be fed.
6. Dressing and Hygiene
 - 4) Normal
 - 3) Independent and complete self-care with effort of decreased efficiency.
 - 2) Intermittent assistance or substitute methods.
 - 1) Needs attendant for self-care.
 - 0) Total dependence.
7. Turning in Bed and Adjusting Bed Clothes
 - 4) Normal
 - 3) Somewhat slow and clumsy, but no help needed.
 - 2) Can turn alone or adjust sheets, but with great difficulty
 - 1) Can initiate, but not turn or adjust sheets alone
 - 0) Helpless.
8. Walking
 - 4) Normal
 - 3) Early ambulation difficulties.
 - 2) Walks with assistance.
 - 1) Non ambulatory functional movement only.
 - 0) No purposeful leg movement.

9. Climbing Stairs
 4) Normal
 3) Slow
 2) Mild unsteadiness or fatigue.
 1) Needs assistance.
 0) Cannot do.
10. Dyspnea
 4) Normal
 3) Shortness of breath with minimal exertion(e.g. walking, talking)
 2) Shortness of breath at rest.
 1) Intermittent(e.g. nocturnal) ventilatory assistance required.
 0) Ventilator dependent.
11. Orthopnea
 4) Normal
 3) Some difficulty sleeping at night due to shortness of breath. Does not routinely use more than two pillows.
 2) Needs extra pillow in order to sleep.
 1) Can only sleep sitting up.
 0) Unable to sleep
12. Respiratory insufficiency
 4) Normal
 3) Intermittent use of BiPAP.
 2) Continuous use of BiPAP.
 1) Continuous use of BiPAP during the night and day.
 0) Invasive mechanical ventilation by intubation or tracheostomy.

2. Modified MRC Grade

Modified MRC Grade	Degree of Strength
5	Normal power
5-	Equivocal, barely detectable weakness
4+	Definite but slight weakness
4	Able to move the joint against combination of gravity and some resistance
4-	Capable of minimal resistance
3+	Capable of transient resistance but collapses abruptly
3	Active movement against gravity
3-	Able to move against gravity but not through full range
2	Able to move with gravity eliminated
1	Trace contraction
0	No contraction