

## PREDICTION OF ISCHEMIC STROKE REHABILITATION OUTCOME USING INITIAL ADMISSION PROTON MAGNETIC RESONANCE SPECTROSCOPY

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### ABSTRACT

**Background:** To predict stroke outcome in advance is important for patients, family supporters, and the community. Imaging has created a means to explore the stroke process in vivo, particularly its underlying pathophysiology and recovery mechanisms. **Objective:** this work was done for prediction of ischemic stroke rehabilitation outcome using 1H-MRS findings with clinical measures of admission. **Methods:** The study included 55 patients with a recent ischemic stroke (mean age, 69±12 years). FIM scores, National Institute of Health Stroke Scale (NIHSS) and 1H-MRS were used for assessment which was done on admission (1st) and after 6 months of rehabilitation (2nd). **Results:** At 1st assessment; N-acetylaspartate from infarcted area/contralateral area (iNAA/cNAA), choline and creatine-phosphocreatine from infarcted area/contralateral area (iCho/cCho and iCr/ cCr respectively) were significantly reduced in all infarcted areas. Lactate was detected in 49/55 patients. Comparing 2nd assessment versus 1st; There were significant increment of iNAA/cNAA, iCr/cCr and iCho/cCho and significant decrement in lactate detection 9/55. Regarding 1st assessment; a significant relation was detected between decreased iNAA/cNAA ratio, lactate detection and decrement of the FIM scores at 2nd assessment. 1st assessment decreased levels of (iNAA/cNAA), (iCho/cCho) and (iCr/ cCr) had significantly positive correlated with the FIM total scores at 1st assessments. Only (iNAA/cNAA) decreased levels had significant positive correlated with the FIM total scores of 2nd assessments. 1st assessment lactate detection and NIHSS high scores had a significant negative correlation with the FIM scores of 1st only. Multiple linear regression analysis was performed. The FIM total score at discharge was significantly influenced by the 1st assessment NAAi/NAAc, lactate detection and NIHSS score. **Conclusion:** 1H-MRS at acute phase may provide prognostic information to the outcome after rehabilitation.

**Key words:** ischemic stroke, 1H-MRS, rehabilitation, outcome, FIM

### INTRODUCTION

To predict stroke outcome in advance is important for patients, family supporters, and the community. Literature surveys show that the strongest and most consistent predictor of stroke rehabilitation outcome is functional ability on admission<sup>(1)</sup>. It has also been reported that the factors of stroke subtypes<sup>(2)</sup>, lesion<sup>(3)</sup>, and cognitive<sup>(4)</sup> affect the stroke outcome. Single-voxel 1HMRS and spectroscopic imaging have been applied to the study of acute ischemic cerebrovascular disease<sup>(5)</sup>. It is capable of measuring levels of N-acetylaspartate, a marker of neuronal function and integrity<sup>(6)</sup>. Reduced N-acetylaspartate (NAA) levels and elevated lactate levels are readily detectable in the

ischemic lesions. Loss of NAA reflects neuronal death and can begin as early as 2 hours after the onset of focal infarction<sup>(5)</sup>. Moreover, the levels of NAA showed additional decline during the subacute phase, probably related to further neuronal loss in the ischemic penumbra<sup>(7)</sup>. High lactate levels can persist a long time after the occurrence of the stroke, but only during the first 24 to 48 hours are they ascribable to anaerobic metabolism<sup>(5)</sup>. However, there are few reports that showed significant relation between rehabilitation outcome and neuronal viability and the metabolic state of the infarcted tissue in the acute stage<sup>(8)</sup>.

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**Aim of work:** predicting ischemic stroke outcome using initial admission 1H-MRS findings with clinical measures.

### MATERIALS AND METHODS

#### Patients

During the study period from January 2010 to May 2011, patients with first ischemic stroke were referred to the rehabilitation unit of the rheumatology and rehabilitation department through the stroke unit of Neurology and Internal medicine departments of Zagazig university, Sharkia governorate. Approximately 70 patients were potentially eligible with the right sort of clinical features during the time of the study, of whom we were able to do spectroscopy in 65 patients. Ten patient were excluded ( one of them was initially classified as having a cortical stroke with clinical and MRI diagnosis of lacunar infarction and nine patients were dead during the period of the study). So we had 55 patients who had an ischemic stroke in the area of the middle cerebral artery (31 males and 24 females, their mean age was  $69 \pm 12$  years; of range, 26-78 years). All had cortical or subcortical lesions greater than 25 mm in diameter. All patients had a new motor or speech deficit and were first examined by combined MRI and single voxel 1H-MRS between 8 hours and 7 days after the onset of symptoms. All patients had physical treatment for six months (three sessions per week. Each session lasts about 45- 60 minutes including exercise protocol for 30 minutes plus Infra red for (15 minutes).

**Control group:** Consisted of 10 (6 males and 4 females) apparently healthy volunteers (no prior or recent history of psychiatric or neurologic disorders) that was confirmed by clinical and laboratory and radiological investigations, they were recruited from patients attending to blood donation unite. Their mean age was  $59.7 \pm 19$  years. Control subjects in the study were used for comparison of the mean metabolite signals between patients and healthy persons so the imaging was performed only once.

#### Inclusion criteria made patients eligible for the present study:

Patients with first and recent ischemic stroke (in 28 patients were during the first 24 hours after the stroke and in 27 during the first week). The diagnosis was based on clinical and neuroradiological examinations with magnetic resonance imaging (MRI).

#### Exclusion criteria:

Subjects unsuitable if they had:

- Cerebral hemorrhage.
- More than one stroke lesion visible on MRI .
- lacunar, or posterior fossa lesions.
- Signs of cerebellar or brain stem injury.
- Prior history of demyelinating or neurodegenerative disorders, and head injury.
- Severe aphasia or poor general clinical status.
- Admitted too late after their stroke.
- Refused to take part in the study or reluctance in sharing in the rehabilitation program.
- Re-stroke during the course of rehabilitation or died.
- Contraindications to MRI (pacemaker, metallic foreign bodies, severe claustrophobia.
- Disturbances of consciousness.
- Presence of other chronic severe diseases or infection that would contraindicate physical therapy.

#### Ethics:

Informed consent was obtained from all patients or from the closest relative, and the experimental protocol was approved by the Ethics Committee of the University of Zagazig, Sharkia , Egypt.

#### Methods:

All patients are subjected

**-Full general and neurological examination** that was done at first and after 6-months follow-up examinations for all subjects.

#### -Laboratory investigation including:

Blood glucose assessment (random, fasting and post prandial)

Complete blood picture.

Lipid profile.

**-Assessment:**

First assessment at the start and second assessment at the end of the rehabilitation program (after 6 months). Assessment included the following parameters:

**A-Measurement of the stroke severity**

By means of the long-term National Institute of Health Stroke Scale (NIHSS) with the following grades: 0–6, mild; 7–15, moderate; and 16–38, severe<sup>(9)</sup>.

**B-Functional assessment:**

It was done by using the Functional independence measure (FIM). Cognitive score is approximately allotted for a quarter of the FIM total score and evaluates communication and social cognition. They are evaluated in 5 items, with a maximum of 35 scores (FIM cognitive), FIM evaluates physical functions are in 13 items, giving a maximum of 91 scores (FIM physical). The total of it is 126 scores (FIM total). Lower scores indicate the worst disability. Clinical utility of the FIM as consecutive scale has been shown by many reports and recognized to be of clinical relevance<sup>(1,3)</sup>.

**C-Imaging assessment:**

Baseline and follow-up MRI and <sup>1</sup>H-MRS imaging was done at the time of each clinical assessment<sup>(10)</sup>.

**1H-MRS Imaging**

We performed for all subjects Single-voxel proton magnetic resonance spectroscopy plus magnetic resonance imaging (MRI) that was done within a maximum of 24 hours, and MRI at 3–7 days, after ischemic stroke in patients group. The MRI and 1H-MRS were performed with a whole body 1.5-T iron-shielded system (Magnetom 63 SP, Siemens AG, Erlangen, Germany) using a standard circularly polarized head coil. A sagittal and a coronal T1-weighted spin-echo sequences (repetition time [TR], 600 milliseconds; echo time [TE], 15 milliseconds) and axial T2-weighted sequences (TR, 2200 milliseconds; TE, 80 milliseconds). The slice thickness was 5mm and the matrix,

256x256. The volumes of interest (VOI) were localized in the ischemic area, taking care to avoid the inclusion of normal tissue or cerebrospinal fluid, and in the corresponding no affected contra lateral region. Local shimming within the selected VOI was required to obtain a spectral width of half of the maximum of the water proton peak of 3 to 6 Hz. The VOIs, ranging between 8 and 16 mL, were targeted from T2-weighted scans. The total examination time for the MRI and the 1H-MRS was less than 60 minutes. The spectrum from the contra lateral region served as the control as for the patient. In the healthy volunteers, the ratios for the metabolite signals from corresponding regions in the right and left hemispheres were almost identical.

**PHYSICAL TREATMENT**

Physical treatment was three sessions per week for a period of six months. Each session was about 45- 60 minutes including exercise protocol for 30 minutes plus superficial heat for the affected side (15 minutes) respecting sensory affection. All patients participated were proceeded in the exercise protocol as well as physical modalities according the clinical and functional condition as well as tolerability of each patient respecting a standardized protocol according to Bruce et al.,<sup>(11)</sup> as follow:

**A- Exercises:**

- Range of motion exercises
- Specific exercises to improve upper and lower limb function
- Learning transfer and mobility
- Balance exercise

**B-Overnight splinting:** A molded plastic orthotic

- For hand fingers and wrist.
- For the ankle and foot.

**C-Improvement in strength and endurance:**

- Progressive aerobic exercises, such as walking on a treadmill three days a week.

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- Have patient exercise with elastic bands, shoulder wheel, step ladder, hand weights or pedal on a recumbent bicycle.

**Statistical Analysis**

The data were tabulated and statistically analyzed using Epi-INFO (2000) and SPSS Version 15 soft were package.<sup>(12)</sup> Demographic data and clinical characteristics are expressed as the mean± standard deviation (SD) for continuous variables and as proportions for categorical variables. Student’s t-test and one-way ANOVA were used as appropriate to analyze group differences. Multiple linear regressions were assessed to explore the independent associated factors of the FIM. The Wilcoxon signed rank test, the Mann-Whitney U test, and the Spearman rank correlation test were used. chi square tests for qualitative data.

**RESULTS**

-Demographic and clinical data of the patients and controls were shown in Table (1).

-There were significant increment of iNAA/cNAA, iCr/cCr iCho/cCho ,

NIHSS and FIM score at 2<sup>nd</sup> assessment. Moreover, there was significant reduction in lactate detection, Table (2).

-A significant relation was detected between the decrement of iNAA/cNAARatio and the worse FIM at discharge (significant lower values). Also patients with lactate detection had significant lower total FIM scores, table (3).

-iNAA/cNAA had significant positive corelation with FIM total scores of 1<sup>st</sup> and 2<sup>nd</sup> assessments (p<0, 01). iCho/ cCho and iCr/ cCr had significant positive correlation with total FIM of 1st assessment only. Lactate detection and reduced NIHSS scores had a significant negative correlation with the FIM total score of 1<sup>st</sup> assessment, Table (4).

-Multiple linear regression analysis with a forward stepwise method was performed. The results show that The FIM total score at discharge was significantly influenced by the NAAi/NAAc(p<0.001), and lactate detection (p<0.001) NIHSS score (p<0.01) (table, 5).

**Table; 1: Demographic and clinical characteristics of the patients.**

Characteristics		Patients group	Control Group
Gender	Female	24(43%)	6(60%)
	Male	31(57%)	4(40%)
Age /years		(69±12)	59.7 ± 19
Initial NIHSS	Mild	36(66%)	-
	Moderate	13 (23%)	-
	Severe	6(11%)	-
Initial FIM	Total	(30±13.9)	-
	Motor	(28.5± 21.3)	-
	Cognitive	(26.2±9.2)	-

Categorical data are expressed in number and percentage continuous data are expressed in mean, SD

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**Table 2: 1<sup>st</sup> assessment versus 2<sup>nd</sup> assessment Proton Magnetic Resonance Spectroscopy (1H-MRS) NIHSS and FIM values.**

Assessment	1H-MRS				NIHSS	FIM
	iNAA/cNAA	iCr/cCr	iCho/cCho	Lac+/-		
First	0.41±0.09	0.53±0.090	0.56±0.29	49/6	22.02±5.1	30±3.9
Second	0.88±0.29	72±0.19	0.62±0.32	9/46	11, 5±201	78.3± 25.9
P	*<0.01	<0.05	<0.05	<0.01	*<0.05	*<0.01

iNAA = N-acetylaspartate from infarcted area; cNAA=N-acetylaspartate from contralateral area; iCr= creatine-phosphocreatine from infarcted area; cCr=creatine-phosphocreatine from contralateral area; iCho= choline-containing compounds from infarcted area; cCho= choline-containing compounds from contralateral area; Lac= lactate;and indicates present; -indicates absent. Data for the 1H-MRS, except for lactate, are expressed as ratios.

Categorical data are expressed in number and percentage continuous data are expressed in mean, SD

**Table 3: FIM at discharge(2<sup>nd</sup> assessment) versus 1H-MRS at admission(1<sup>st</sup> assessment)**

		N (%)	Mean	P
iNAA/cNAA	Decreased	36(65)	52.01± 1.33*	<0.001
	Not decreased	19(35)	73.49±1.22	
iCr/cCr	Decreased	46(83)	70.58±1.54	0.187
	Not decreased	9(17)	72.91±1.65	
iCho/cCho	Decreased	21(38)	72.86±1.55	0.07
	Not decreased	34(62)	69.49±1.55	
Lactate	Detected	49(89)	54.44±1.12*	<0.01
Lactate	Not detected	6(11)	82.01± 1.10	

**Table 4: Correlation between parameter in 1<sup>st</sup> assessment and FIM total and NIHSS of 1<sup>st</sup> and 2<sup>nd</sup> assessments .**

Parameter in first assessment	1 <sup>nd</sup> assessment		2 <sup>nd</sup> assessment	
	FIM Total	NIHSS	FIM Total	NIHSS
<b>iNAA/cNAA</b>	0.375**	0.219*	0.495**	0.127 *
<b>iCr/ cCr</b>	0.213*	0.015	0.109	0.112
<b>iCho/cCho</b>	0.200*	0.195	0.111	0.132
<b>Lactate detection</b>	0.328*	0.230*	0.015	0.117
<b>NIHSS</b>	-0.219*	-	-0.195	0.111

\*P,<.0.05

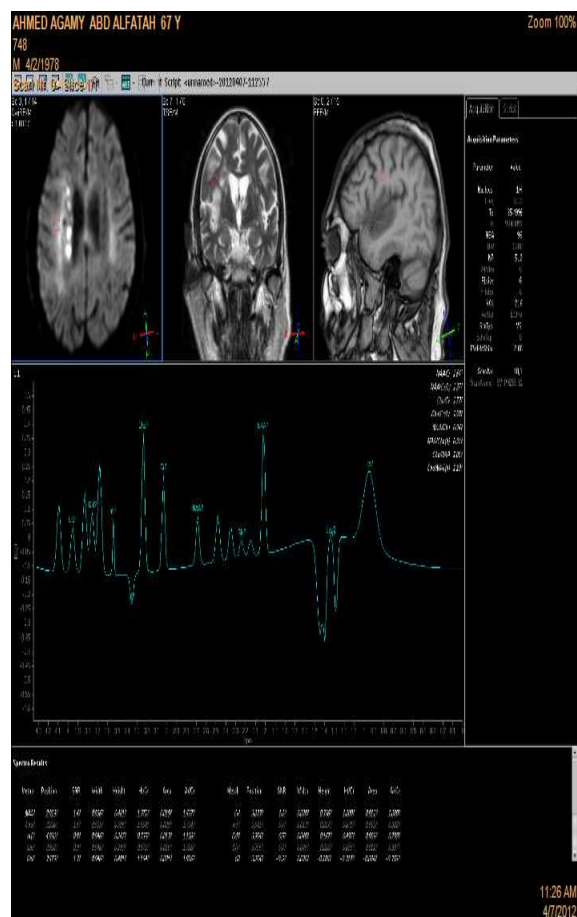
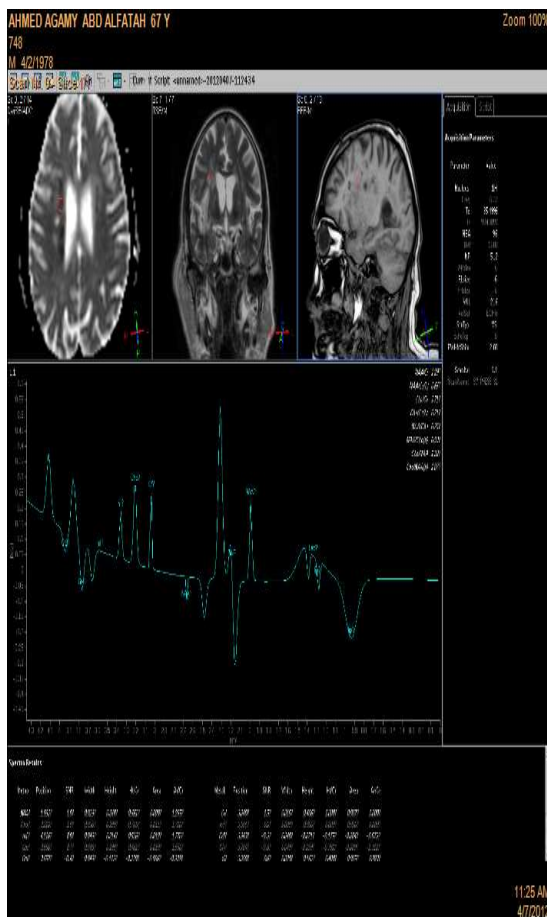
\*\*P<.0.01

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**Table 5: Multiple regression analysis for factors influencing the Total FIM of 2<sup>nd</sup> assessment**

Variable	Adjusted R2	Standardised coefficients (B*)	95%CI	t	P value
Reduced iNAA/cNAA	0.500*	-0.60	-3.81-2.95	-15.801	<0.001
Lactate detection	0.544 <sup>Δ</sup>	-0.25	-0.83- -0.39	-5.464	<0.001
Increased NIHSS	0.560 <sup>□</sup>	-0.12	-0.19- -0.07	-4.440	0.01

\*Predictors: (constant), iNAA/cNAA  
 ΔPredictors: (constant), iNAA/cNAA, lactate.  
 □Predictors: (constant), iNAA/cNAA, lactate, NIHSS.  
 xDependent variable: FIM Total.  
 Model constant=136.55



Single-Voxel Magnetic resonance spectroscopy imaging of a patient with ischemic stroke done within 24 hours after onset of symptoms, appeared by DWI as hyperintense area in the left basal ganglia (A) Single-voxel spectroscopy of the lesion shows an elevated lactate, choline and creatinine compared with the contralateral side ( B) Abbreviations: Cho, choline; Cre, creatinine; Lac, lactate; NAA *N*-acetylaspartate

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**DISCUSSION**

The mechanism of rehabilitation efficacy may depend on several variables, including the rehabilitation approach, neural status of the patient, and time post-stroke. This work was done for prediction of ischemic stroke rehabilitation outcome using 1H-MRS of admission.

We detected reduction of iNAA/cNAA, iCho/cCho and iCr/CCr in acute infarctions (during 1<sup>st</sup> assessment). One explanation for this finding is accelerated lipid synthesis involved in myelin repair or may be attributable to considering *N*-acetylaspartate as a temporary source of cellular energy locally at the site of axonal injury, which would produce a transient decrease that might precede any loss of *N*-acetylaspartate as a result of axonal death<sup>(13)</sup>. On the other hand one study<sup>(14)</sup> reported increment of Cho levels, they stated that the increased levels may be caused by an elevated turnover of membrane lipids, but this study did not select patients in the acute stage.

In the present study detected lactate signal from the infarcted areas was significantly more during 1<sup>st</sup> than 2<sup>nd</sup> assessments. Lactate presence has been related to multiple factors, including excessive release of glutamate, impaired aerobic glycolysis, disordered mitochondrial and oxidative metabolism, and systemic responses to trauma<sup>(15, 16, 17)</sup>.

Patients with better outcome ( 2<sup>nd</sup> assessment higher FIM scores) in the present study had relatively preserved NAA and undetectable lactate. This findings met with the finding of another study<sup>(15)</sup>.

We found a significant positive correlation between reduced iNAA/cNAA of 1<sup>st</sup> assessment and the FIM total score at discharge which met with another study<sup>(9)</sup> which stated that a more pronounced reduction of the level of NAA inside ischemic lesions, apparently evident to a similar degree in MRI, can suggest a more serious neuronal loss. One possible explanation for this variability is that while

1H-MRS may detect only neuronal loss, MRI may be influenced by cellular edema. We found also that decreased levels of Cho and Cr during 1<sup>st</sup> assessment had a significant positive correlation with the FIM scores of 1<sup>st</sup> assessment only. One possible explanation for that is the less marked variations of their levels at 1<sup>st</sup> assessment NAA that was in agreement with another study<sup>(11)</sup>. In the present study, there was significant negative correlation between the level of lactate during the acute phase and FIM scores. This significant difference was no longer evident during the chronic phase. These results indicate that spectroscopy performed as soon as possible after stroke can have a prognostic value, especially when the reduction in the level of NAA and the presence of lactate are considered.

We found that INAA/cNAA value showed the highest correlation to the total FIM scores of 2<sup>nd</sup> assessment. It was interesting that INAA/ cNAA ratios were more significantly predictive than lactate detection. One possible explanation for that is decreased Nacetylaspartate/ creatine ratios reflect neuronal injury or dysfunction resulting from both traumatic and ischemic injury, whereas lactate reflects hypoxic-ischemic injury only<sup>(11)</sup>. Another study<sup>(8)</sup> did not find clear correlation between the levels of NAA and lactate during the acute phase of stroke and the clinical outcome. However, these studies involved too few patients to determine the significance of prognostic information.

**CONCLUSION**

Clinical evaluations including the initial FIM and NIHSS may be a simpler method to predict rehabilitation outcome. However, our results using H1MRS studies are more important for physical independence. Therefore, objective examinations such as H1MRS might be a predictor of potential recovery in rehabilitation.

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## مأل نتيجه اعاده تاهيل السكته الدماغيه الاحتشائيه باستخدام الرنين المغناطيسى الطيفى

اعاده تاهيل السكته الدماغيه هى الطريقه التى بها مرضى السكته الدماغيه يعالجون للعودة الى حياتهم الطبيعيه بقدر الامكان لذلك اجريت هذه الدراسه فى قسم امراض المخ و الاعصاب و قسم الروماتيزم و التاهيل فى مستشفيات جامعه الزقازيق فى الفترة من يناير ٢٠١٠ الى مايو ٢٠١١ على ٥٥ مريضاً يعانون من السكته الدماغيه الاحتشائيه (٣١ سيدة (٢٤ رجل) تتراوح اعمارهم ما بين ٢٦ و ٧٨ سنه و تم عمل الاتى :-

١ - اخذ التاريخ المرضى للمرضى

٢- فحص اكلينيكي شامل

٣- فحص عصبى شامل

٤- التحاليل المعملية

٥- اشعه بالرنين المغناطيسى الطيفى عند دخول المرضى و بعد سنه اشهر من المتابعه

٦- علاج طبيعى (بروتوكول) اعاده تاهيل خاص بالمرضى

و تم تقييم هولاء المرضى بمقياسين هما ١-مقياس الاعتماد الوظيفى ٢- و مقياس معهد الصحة الوطنى للسكته الدماغيه فى بدايه المرض و بعد سنه اشهر ايضا من المتابعه و قد خلصت هذه الدراسه ان الاسيتايل اسيرتيت و الكولين و الكرياتين فوسفو كرياتين سجلوا انخفاضاً ملحوظاً فى كل مواضع الاحتشاء وكان ذو دلالة احصائيه واضحه ووجدت مادة اللاكتيت فى ٤٩ مريضاً و وجد ان هنالك علاقه وطيدة بين معدل انخفاض الاسيتيل اسيرتيت و مقياس الاعتماد الوظيفى و مقياس معهد الصحة الوطنى للسكته الدماغيه ووجد ان المرضى الموجود بهم مادة اللاكتيت سجلوا انخفاضاً فى مقياس الاعتماد الوظيفى عنه فى المرضى الغير الموجود بهم مادة اللاكتيت وتمثل نسبة الاسيتايل اسيرتيت فى منطقة الاحتشاء والمنطقه المقابله السليمه من المخ علاقه واضحه مع مقياس الاعتماد الوظيفى و مقياس معهد الصحة الوطنى عن النسبه ما بين الكرياتين فوسفو كرياتين فى التقييم الثانى ولذلك عمل الرنين المغناطيسى الطيفى فى المرحله الاولى السكته الدماغيه الاحتشائيه يعطى معلومات تنبؤيه عن المال بعد اعاده التاهيل