v. 3, n. 27, 2023

International Journal of Health Science

HYPOINTENSITY OF THE MOTOR CORTEX IN THE SUSCEPTIBILITY WEIGHTED SEQUENCE: A RADIOLOGICAL BIOMARKER OF AMYOTROPHIC LATERAL SCLEROSIS?

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Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the progressive loss of upper and lower motor neurons (AMN) and resulting in loss of voluntary control of movement. The presence of hyposignal in the motor cortex on the magnetic susceptibility sequence (SWI) may indicate a lesion in the SMN. The aim was to verify the presence of hyposignal in the motor cortex on cranial magnetic resonance (MR) SWI in patients diagnosed with ALS. This is a descriptive study that evaluated data from 20 ALS patients and 20 controls. The statistical significance of the variables was verified using the t test and the linear regression test, with alpha levels of 0.01 and 0.05, respectively. Clinical variables did not statistically influence the presence of hyposignal in the motor cortex of patients with ALS, but in the control group there was statistical significance of age in the presence of hyposignal, being more present in the elderly. When comparing the presence of hyposignal in patients with ALS and healthy individuals, there was a static difference, being more frequent in patients with ALS. There was also a statistical influence of MT hypersignal on the presence of hyposignal in the motor cortex in SWI. It was concluded that the presence of hyposignal in the motor cortex of patients with ALS is not influenced by clinical variables, despite being more frequent in patients with ALS than in healthy individuals. Age can influence the presence of hyposignal in healthy individuals, but in the ALS group there was no such relationship, which may suggest neurodegeneration. Patients who had hyposignal in the cortex also had hypersignal in the LMCA, which would make it possible to use the SWI as another tool for detecting lesions in the SMN and, thus, help in the final diagnosis of ALS.
Keywords: Amyotrophic lateral sclerosis; diagnostic imaging; motor neuron disease

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of the central nervous system that is characterized by the progressive loss of motor neurons in the cerebral cortex and spinal cord, resulting in muscle paralysis and loss of voluntary control of movement.

The prevalence of ALS in the world is 6 cases per 100,000 inhabitants and the incidence is 1.5 to 2.6 per 100,000 inhabitants, increasing after 40 years of age, with a peak between 60 and 75 years of age. Although low, the prevalence of ALS has been increasing worldwide, due to better health care and medical care in general, which facilitates diagnosis (MOURA, 2016).

In Brazil, a study carried out in 2016 by MOURA et al reveals that between 45 and 82 years of age, the incidence was 2.3 cases per 100,000 inhabitants in 2013. According to the study by AVILA and MONSORES in 2016 on mortality of rare diseases in Brazil, ALS was one of the main causes of death.

Considered a disease with unknown causes, although there are hypotheses of genetic influence, such as, for example, the mutation of the catalytic enzyme superoxide dismutase (SOD-1). Currently more than 120 mutations have been linked to ALS. Other causes have also been suggested, such as changes in immunity, physical trauma, persistent viral infections and chemical environmental factors (SANTOS, 2017).

Changes related to the upper motor neuron (UMN) are hypertonia, hyperreflexia and spasticity. Symptoms related to changes in the lower motor neuron (LMN), anterior horn cells of the spinal cord, brainstem nuclei and some cranial nerves are progressive muscle weakness with fasciculations and cramps (DOMINGOS, 2017).

The diagnosis of ALS is evident in patients with a long course of the disease, but early diagnosis, when there are only focal symptoms in one or two regions, will depend on several serial investigations. From the onset of symptoms to the definitive diagnosis, there is, on average, a time of 10 to 13 months (SANTOS, 2017).

ALS is a disease diagnosed clinically after excluding other causes of progressive loss of upper and lower limb function. However, the diagnosis can be difficult due to the variety of clinical manifestations and the absence of a specific test for confirmation (SANTOS, 2017).

There are standardized criteria that help to exclude the disease. In 1990 the World Federation of Neurology standardized the El Escorial criterion for diagnosing ALS and in 1998 it was improved and became known as El Escorial Revisto or Airlie House criterion. They classify ALS as clinically defined, probable, probable with laboratory support and possible (SANTOS, 2017).

In 2000, a group of experts in ALS and electroneuromyography created a set of criteria called AWAJI, which significantly increased the ability to diagnose patients with ALS. It is taken into account that electrophysiological changes have the same value as clinical signs of lower motor neuron alteration (SANTOS, 2017).

Magnetic resonance imaging (MRI) is the main neuroimaging study of the brain and spinal cord, being useful to exclude syndromes similar to ALS, such as multiple sclerosis, stroke, tumors and radiculopathies. When associated with ALS, MRI can reveal abnormal signals in the motor pathways from the motor cortex to the brainstem, with hyperintensity of the cortico-spinal tract in T2 and FLAIR being the most characteristic alteration (CAVACO, 2016). However, this alteration was also observed in patients without a diagnosis of ALS, as mentioned in the work by ROCHA (2012) and demonstrated in studies by ROCHA (2002).

The transfer magnetization sequence (TCM) is widely used to evaluate lesions in the spinal cortical tract in patients with ALS, through the identification of structural alterations in the tissue, thus leading to changes in signal hyperintensity on MRI (ROCHA, 2012). The effect of this sequence depends on the ratio of relative water to macromolecular concentration. Thus, a low ratio indicates damage to myelin or the axonal membrane, therefore being able to detect lesions in the cortico-spinal tract (ROCHA, 2012).

The susceptibility-weighted sequence (SWI) of MRI demonstrates the differences between tissues that contain deoxygenated paramagnetic blood products, such as deoxyhemoglobin and hemosiderins, and healthy tissue. It also reveals the presence of mineral deposits such as calcium and iron. When compared with conventional MRI sequences, SWI gives a better anatomical definition of iron deposits in mesencephalic structures and the medial geniculate body (LIMA, 2011).

According to YU et al (2014), when analyzing the SWI sequence in patients with ALS, they showed an increase in the iron level in the cerebral motor cortex, thus being a reliable method to test the iron level. In the study by LIBERATO (2015) it was proposed that iron accumulation is related to hypointensity in the gray matter of the precentral gyrus in SWI, thus being a possible biomarker for ALS.

In the study by IGNJATOVIC et al (2013) it is mentioned that abnormal levels of iron in the CNS are known in several neurodegenerative diseases, including ALS. He compared 45 patients with ALS and 26

negative control patients, resulting in 42 patients with signal hypointensity in the precentral gyrus of the gray matter.

Oxidative stress is considered a mediator of neurodegenerative diseases, including ALS, which leads to dysregulation of iron levels. However, oxidative stress can be triggered by increased iron levels, so studies are still being carried out in order to better elucidate the pathophysiology (MIRANDA, 2016). According to DEVOS (2020), iron accumulation appears before neuropathology and is maintained during the progression of the disease, in addition to considering the high ferritin level a predictor of poor prognosis.

According to MIRANDA (2016) the SOD1 mutation, present in familial ALS, leads to the production of reactive oxygen species (ROS) and these increase the levels of iron regulators, such as ferritin and transferrin, thus deregulating the metabolism of this metal.

According to the study by WANG (2019), the increase in oxadative stress can be evidenced by the presence of markers in the peripheral blood of patients with ALS, through the dosage of malondialdehyde (MDA), 8-hydroxyguanosine. In the work published by ROBELIN (2014) numerous markers were mentioned, such as the reduction of catalase and glucose-6-phosphate dehydrogenase activity, as well as the serum level of uric acid, such substances are considered antioxidants. In that same study, high levels of 8-hydroxyguanosine, nitric oxide and ferritin and low levels of transferrin were reported in the peripheral blood of patients with ALS, suggesting an alteration in iron metabolism that can lead to toxicity.

The SWI sequence was created in 1997 with the aim of measuring the level of iron and other substances that alter the magnetic field, however it was only widely used clinically after 10 years. With the greater acceptability of this sequence, many software programs include it as a way to obtain more information on diseases, especially neurological ones, such as multiple sclerosis, stroke, brain tumors and neurodegenerative diseases (ADACHI et al, 2014).

It is known that the iron content in the brain increases with age, mainly in the basal ganglia. But, it also increases in many neurodegenerative diseases such as Parkinson's disease, Huntington's disease, Alzheimer's disease and Amyotrophic Lateral Sclerosis. The difference in iron between white and gray matter is well analyzed in some brain regions, such as the motor cortex, for example. The ability to measure the amount of iron can help in understanding the progression of these diseases, as well as in the response to treatments, since it is directly related to oxidative stress and neuronal death ADACHI et al (2014).

Many studies, such as that by ADACHI et al (2014), consider the SWI sequence to be sensitive to detect hyposignal in the motor cortex in patients with ALS. In his study, he verified the presence of hyposignal and the presence of ferritin deposits, which bind to ferric iron, in the cortex of patients after death. The imbalance of this form of iron is closely linked to neuronal death by oxidative stress.

Thus, the use of the MRI SWI sequence helps to verify the involvement of the upper motor neuron in patients with ALS, since, many times, the symptoms and signs of the lower motor neuron overlap in the neurological examination, making the definitive diagnosis of the disease difficult.

METHODOLOGY

All subjects in this research were studied after approval by the Research Ethics

Committee of the Hospital Ophir Loyola (HOL). The research was authorized by the work supervisor and by the interviewees, through an Informed Consent Form, after communicating the purpose of the study, ensuring their anonymity.

Characterized as a cross-sectional descriptive study with a qualitative approach. The research casuistry consisted of 20 patients enrolled in the Neurology clinic of the HOL diagnosed with ALS and 20 subjects for the control group, volunteers, paired in sex and age with the patients, healthy, that is, without previous neurological diseases.

Data collection was obtained through the analysis of the MRI of the skull, by a neuroradiologist, performed in patients with ALS and the control group on predetermined days, according to the availability of the researchers and analyzed subjects, in the period of October 2021 to December 2021. MTC and SWI sequences of all patients were analyzed. The cranial MRI examination was carried out in the Division of Diagnostic Imaging of the HOL (DDI).

Clinical history and neurological examination were performed by neurologists in all patients. All patients underwent diagnostic, laboratory and imaging tests to exclude other diseases that mimic motor neuron disease. The diagnosis of amyotrophic lateral sclerosis of all patients was based on the revised El Escorial criteria and on the recommendations of the Awaji-shima consensus that consider clinical and electrophysiological findings. All patients in the control group had a normal neurological examination.

Images were acquired in a 1.5 tesla device with a number of independent receiver channels. T1 spin-echo (SE) sequence with additional magnetization transfer pulse (TM) with 05 mm slice thickness and magnetic susceptibility sequence with 01 mm slice thickness were used, both in the axial plane.

Subjective analysis of the signal from the motor cortex in the precentral gyrus was performed and compared with the adjacent cortex in the postcentral and middle frontal gyri, with analysis being performed by a neuroradiologist accustomed to interpreting these two pulse sequences. In the SWI sequence, it was analyzed whether there was hyposignal in the motor cortex and classified into three levels: 0 (absent), 1 (mild) and 2 (marked), after comparing with the underlying postcentral cortex. The motor cortex region was identified using the identification of the omega signal as a parameter. In the MTC sequence, it was analyzed whether there was hypersignal in the supratentorial cortical spinal tract.

Clinical and epidemiological data were collected from patients' charts. T-test, U-test and linear regression test were used. In the T and U tests, the null hypothesis rejection index was set at 0.05 or 5%, significant values being marked with an asterisk (*) and the regression test at 0.01 or 1%.

RESULTS

Diagnosis, based on El Escorial's revised criteria, was as follows: 18 patients with definite ALS, 2 patients with probable ALS. All patients, regardless of the defined diagnosis, had had the disease for more than 1 year. Age and sex did not differ between patients and controls, all aged between 40 and 80 years. 12 ALS patients had motor onset and 8 bulbar symptoms. Clinical and epidemiological characteristics are described in table 1.

In resonance images with SWI sequence of patients with ALS, the presence of hyposignal in the precentral gyrus was verified in 9 patients. In the resonance images with MTC sequence, hypersignal was verified in the cortical spinal tract of 9 ALS patients, which were not the same ones verified in the SWI sequence. The presence of hyposignal was

PATIENT	TIME OF DISEASE (months	AGE (years)	DIAGNOSIS	SUBTYPE	SIGN IN NMS	GENDER	FUNCTIONALITY
1	25	53	DEFINITIVE	MOTOR	YES	M	2
2	69	63	DEFINITIVE	MOTOR	NO	M	1
3	13	48	DEFINITIVE	BULBAR	NO	F	5
4	27	60	DEFINITIVE	MOTOR	YES	F	1
5	36	48	DEFINITIVE	MOTOR	YES	M	3
6	20	44	DEFINITIVE	MOTOR	YES	M	1
7	24	60	DEFINITIVE	MOTOR	YES	F	1
8	15	67	DEFINITIVE	MOTOR	YES	M	1
9	36	70	DEFINITIVE	BULBAR	YES	M	3
10	26	68	DEFINITIVE	BULBAR	NO	F	1
11	27	66	DEFINITIVE	MOTOR	YES	F	3
12	24	42	DEFINITIVE	BULBAR	YES	F	4
13	30	61	DEFINITIVE	MOTOR	YES	F	5
14	33	64	DEFINITIVE	BULBAR	YES	F	3
15	60	56	DEFINITIVE	MOTOR	YES	F	5
16	24	47	DEFINITIVE	BULBAR	YES	F	4
17	40	70	DEFINITIVE	BULBAR	YES	M	1
18	24	65	DEFINITIVE	MOTOR	YES	M	2
19	12	48	DEFINITIVE	MOTOR	NO	M	3
20	48	74	DEFINITIVE	BULBAR	YES	M	3

Table 1. Clinical and Epidemiological Characteristics of ALS Patients.

Source: research database.

verified in the motor cortex of 1 control patient.

ALS patients were classified into three levels of motor cortex signal reduction in the SWI sequence: 11 with classification 0 (figure 1A); 6 with classification 1 (figure 1B) and 3 with classification 2 (figure 1C). The control group was also classified into levels: 19 with level 0 (figure 2A) and 1 with level 1 (figure 2B), the latter being 80 years old. Regarding the MTC sequence, 9 ALS patients had increased signal in the spinal cortical tract (figure 3)

In statistical analysis, using the U test, with healthy subjects, ALS patients had more signal reduction in the motor cortex, that is, the presence of hyposignal depends on the diagnosis of ALS ($p<0.05$).

The age of patients with ALS does not interfere with the presence or absence of hyposignal, T test ($p> 0.01$) (graph 1). In the control group, only the oldest patient had such alteration (graph 2), therefore, with age interference, T test ($p< 0.01$).

Of the patients with positive SWI, 5 had some independence to carry out their basic life activities (SINAKE & MULDER functionality grade 1 and 2). Of those with negative SWI, 4 had some independence. After analysis by the T test, there was no statistical interference of functionality in the presence of hyposignal in SWI ($p>0.01$). When analyzing whether the level of hyposignal influenced the degree of functionality (based on the severity of the disease), there was no statistical influence (graph 03), regression test ($p>0.05$).

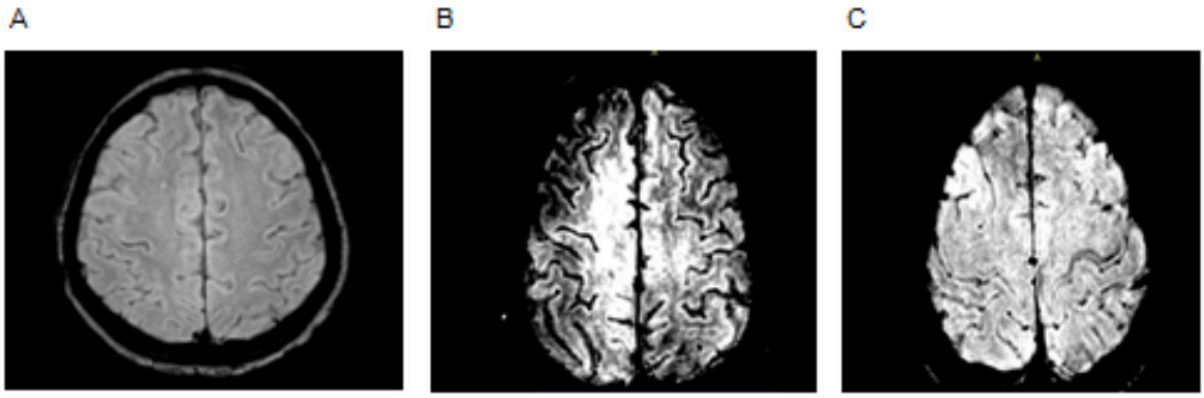


Figure 1 - hyposignal levels in the motor cortex of ALS patients. SWI sequence. level zero; B: level 1; C: level 2.

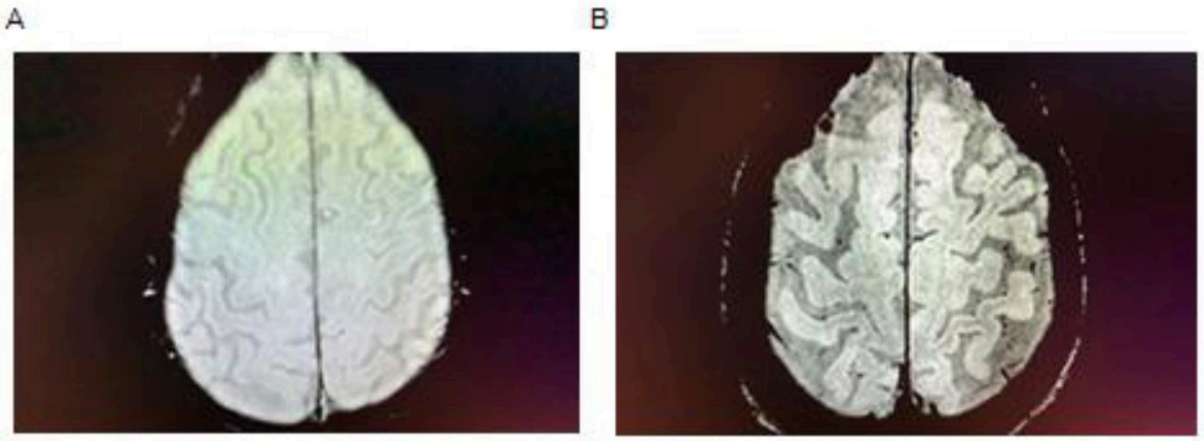


Figure 2: Hyposignal levels of control subjects. SWI. A: level zero; B: level 1.

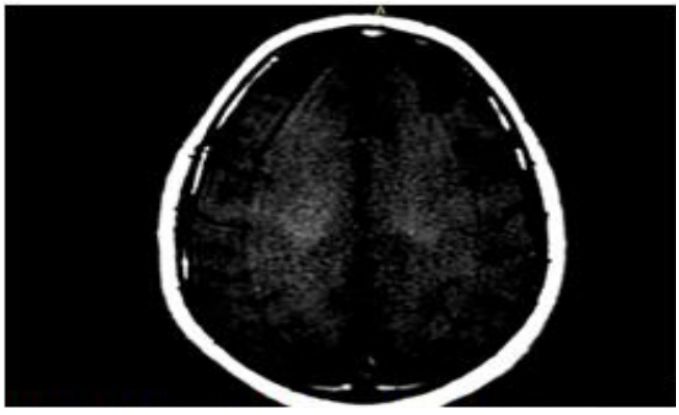
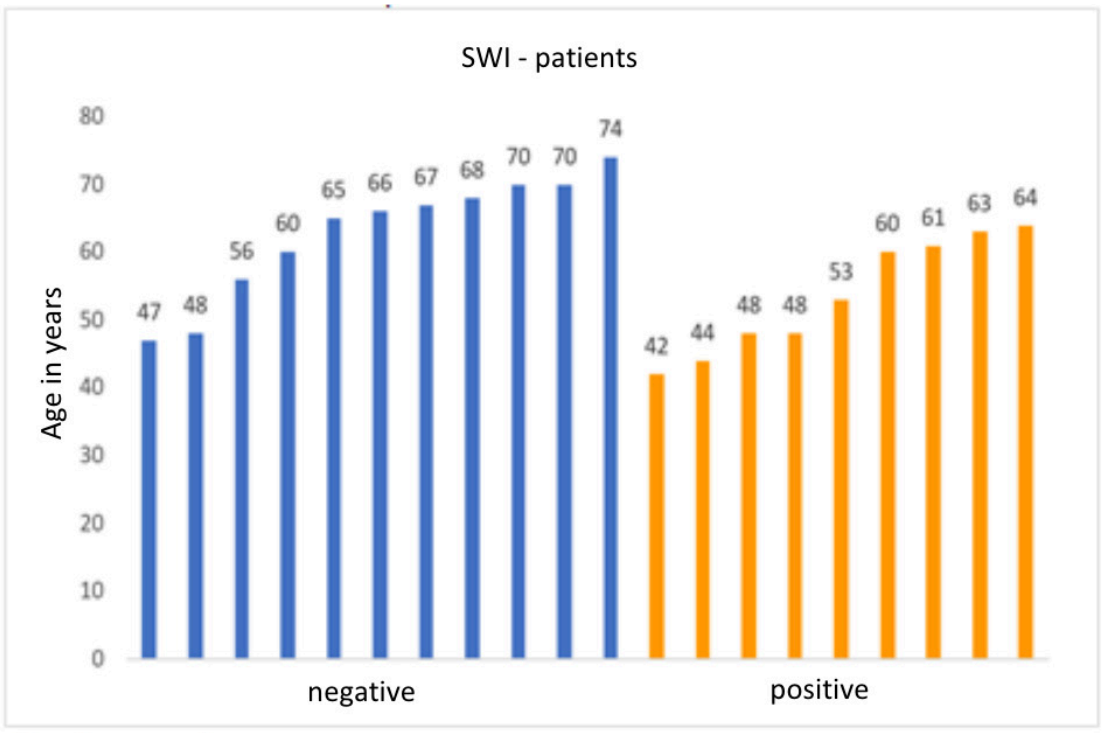
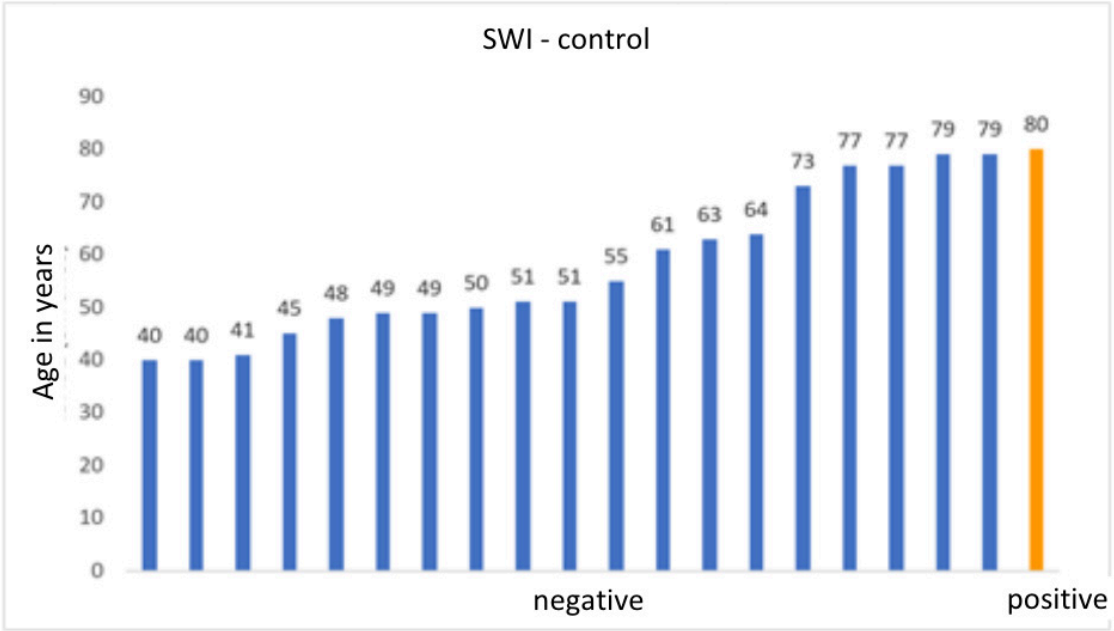


Figure 3: Hypersignal in TCM ALS patients.



Graph 1 - Age of ALS patients and SWI result.

Source: author.



Graph 2 - Age of controls and SWI.

Source: author.

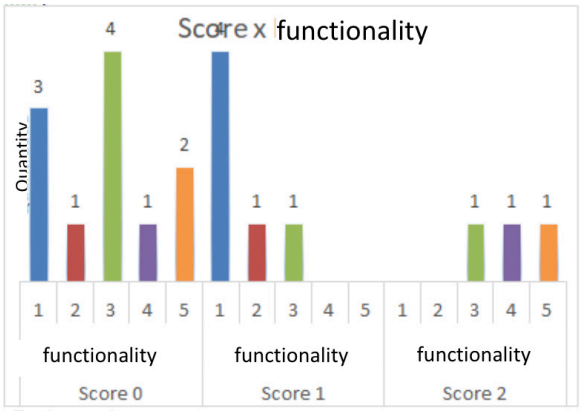
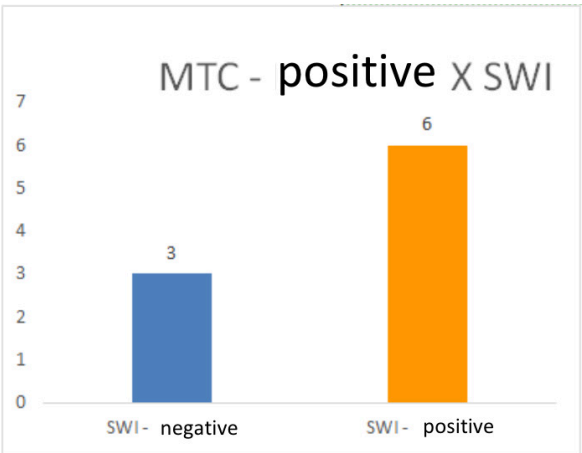


Chart 03 - Relationship between hyposignal level and functionality in ALS patients.

Source: author.

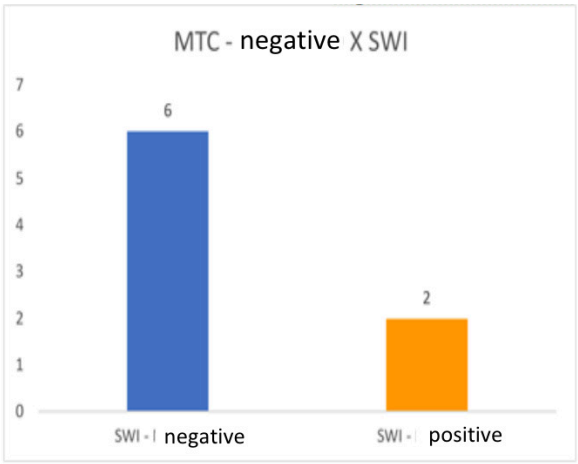
Of the 9 patients with ALS, 4 had no signs of upper motor neuron injury, 2 without hyposignal and 2 with hyposignal in SWI. After statistical analysis using the linear regression test, it was observed that the variables are not dependent ($p>0.05$).

Of the patients with hypersignal in MTC or hyposignal in SWI, 6 had both alterations and of the patients without hypersignal in TCM, 3 had hyposignal in SWI (graphs 4 and 5). After statistical analysis, using the linear regression test, it was observed that the SWI variable depends on the MTC variable ($p<0.05$).



Graph 8 - ALS patients with positive TCM and SWI result.

Source: author.



Graph 9 - ALS patients with negative TCM and SWI result.

Source: author.

DISCUSSION

The findings of this study showed that ALS patients are more likely to change the signal in the motor cortex than healthy individuals. This finding is consistent with the pathophysiology of the disease, where there is iron deposits in the motor cortex due to increased oxidative stress, which is in line with the studies by SCHWEITZER et al (2015) and YU et al (2014).

It is suggested that the iron deposited in the cortex of these patients is linked to ferritin and not to hemosiderin, the former being deleterious to microglial cells. Ferritin is related to neurogenerative diseases such as Alzheimer's, Parkinson's disease and ALS, whereas hemosiderin is related to vascular diseases such as hemorrhagic stroke, amyloid angiopathy and cavernous hamangioma (ADACHI et al, 2014; KWAN et al, 2012).

ALS patients with initial motor presentation did not obtain a significant difference from those with bulbar onset, regarding the presence of low signal, in this study. This fact is in line with the findings of IGNJATOVIC et al (2013) and YU et al (2014). Although a higher frequency of hyposignal is expected in patients with

bulbar onset, since this type of presentation is more aggressive and affects motor neurons more quickly.

The patients' age had no significant influence on the presence of hyposignal in SWI, but in the control group, age was statistically relevant, that is, the older the healthy subject, the greater the chance of hyposignal in the motor cortex. This study is in line with that of ADACHI et al (2014) and KWAN et al, 2012. This is explained by the high level of metabolism in this region, but the accumulation of iron is not found in the motor cortex of individuals under 65 years of age. Therefore, it is presumed that the accumulation of iron in the motor cortex of ALS patients is related to neurodegeneration (KWAN et al, 2012).

The presence or absence of hyposignal did not depend on the duration of the disease in this study. What corroborates the findings of YU et al in 2014, ADACHI et al (2014). However, all patients with positive SWI for the presence of hyposignal had a definitive diagnosis of ALS.

The influence of the degree of functionality in the presence or absence of low signal was not verified, as in the studies by YU et al 2014. The hyposignal score also did not influence the degree of dependence of the patients, which is not in line with the findings of SCHWEITZER et al (2015) and IGNJATOVIC et al (2013). It was expected that patients more dependent for their basic activities would have more hyposignal, since with the progression of the disease and the increase in its severity, there is greater neuronal death and, consequently, more oxidative stress and iron accumulation.

The presence or absence of upper motor neuron signals had no statistical relationship with the presence of hyposignal, which contradicts the findings of COSTAGLI, et al (2016), which showed hyposignal in the motor cortex mainly in ALS patients with signs of impairment of the motor cortex. upper motor neuron, which is plausible, since this region of the CNS is a topographical representation of these clinical signs.

In this study, it was observed that the presence of hyposignal in SWI in patients is directly linked to the presence of hypersignal in the cortico-spinal tract in the MTC sequence. In the study by COSOTINI, et al (2010), the presence of low transfer magnetization in the motor cortex of ALS patients was observed, which may justify the findings of this work. It is known that MTC is a highly sensitive (80%) and specific (100%) sequence for detecting upper motor neuron lesions (ROCHA, 2012), therefore, its correlation with SWI can infer that the latter is a good tool of diagnostic aid in lesions in the NMS.

Alterations in the lower motor neuron can mask the clinical signs of injury in the SMN, so it is necessary to use a complementary tool that detects this injury. In this context, the SWI sequence can help guide the diagnosis of patients with amyotrophic lateral sclerosis. More studies are needed to confirm this hypothesis. The study by IGNJATOVIC et al (2013), considers promising the use of signal hypotension in the motor cortex as a biomarker for ALS.

As limitations of this work, there is the use of 1.5T MRI, since the use of 3T increases the chance of detecting the alterations studied by reducing noise, in addition to the use of a form of alteration detection, the visual scale. Another important limitation was the inclusion of patients without a definitive diagnosis, as this may reduce the chance of hyposignal in the motor cortex.

It was not possible to perform the MTC sequence in control individuals, which made it difficult to compare the two sequences and a possible analysis of sensitivity and specificity.

CONCLUSION

It can be concluded that the presence of hyposignal in the motor cortex is associated with the diagnosis of ALS, but the presence of this signal is not influenced by the clinical presentation, disease duration, disease severity, clinical signs of upper motor neuron injury and age, the latter influencing only healthy individuals.

It is also concluded that the SWI sequence is still little explored as an aid in the diagnosis of ALS, with even few studies on the subject, but those who dedicate themselves to studying it, consider it an important tool and consider it as a tool. future biomarker of ALS, as it shows damage to the upper motor neuron. This statement is also considered by this author.

Many studies still need to be done for this signal change to become established as a biomarker in amyotrophic lateral sclerosis.

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