SERUM LEVEL OF RETINOL BINDING PROTEIN 4 IN RELATION TO AMYOTROPHIC LATERAL SCLEROSIS AMONG EGYPTIAN PATIENTS

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ABSTRACT:

Background: *Amyotrophic lateral sclerosis is a progressive devastating neurodegenerative disorder. It is characterized by both upper and lower motor neuron degeneration, leading to progressive skeletal muscle atrophy, paralysis, and consequent death. The pathogenesis of ALS and the risk factors are still not fully understood. Yet, metabolic abnormalities and nutritional factors have been recently the focus of interest among the various aspects of consideration. Vitamin A metabolite; Retinoic acid plays an important role in motor neuron development and neurite regeneration and its only carrier protein is retinol-binding protein 4.*

Aim of the work: *This study aimed to measure the serum level of retinol-binding protein4 (RBP4) and to investigate the association between the clinical aspects of ALS and serum retinol-binding protein 4 (RBP4) concentration as a potential biomarker for vitamin A metabolism in ALS patients.*

Subjects and methods: *This is a case-control study performed in the neuromuscular unit, Neurology Department, Ain-Shams University hospital. The study period was one year. Forty ALS patients were recruited and matched with forty healthy controls of matched age and sex. A Quantitative determination of human retinol-binding protein 4 concentrations in serum was assayed by Quantikine ELISA kit (2017 R & D Systems, inc.).*

Results: *Serum RBP4 level was statistically non significantly higher among the control group versus the ALS group.*

Conclusion: *Serum RBP4 concentration was found to be lower although statistically nonsignificant in ALS patients than in the controls group, further studies are needed.*

Keywords: *Amyotrophic, Sclerosis, RBP4, Vitamin A.*

INTRODUCTION:

Amyotrophic lateral sclerosis (ALS) is a progressive fatal neurodegenerative disease. It is characterized by motor neuron degeneration in the brain and spinal cord **(1)** resulting in death within 3 to 5 years of onset and Its incidence worldwide is 1 in 50,000 / year. Male to female ratio is 1.5 **(2)**. ALS typically begins in the limbs but one-third of cases present with bulbar onset, in the form of difficulty in speaking, chewing, and swallowing sparing the ocular and sphincters innervation till the late stages **(3)**. ALS is a clinically diverse illness with distinct motor and non-motor symptoms. The motor signs of the disease are quite variable, and they may be associated with various degrees of frontotemporal

involvement. It is recognized as a complex multi-system disease that arises from a combination of genetic susceptibility and environmental exposure [(1)].

On the other hand, several studies showed that there is a relation, either directly or indirectly, between ALS and retinoic acid [(4&5)]. Retinoids play a crucial role in cellular differentiation, programmed cell death, and other vital cellular functions. Regarding the nervous system, retinoids seem to be essential in the induction of neural differentiation, motor axon outgrowth, and neural patterning. Also, elevated RA signaling correlates with axon outgrowth and nerve regeneration [(6)]. Moreover, recent investigations suggest that retinoids could contribute to modulating protein metabolism through promoting cellular tolerance to circumstances characterized by proteasome inhibition[(7&8)].

Vitamin A is a group of fat-soluble retinoids, including retinol, retinal, and retinyl esters. It originates in diet either as preformed vitamin A (retinol and its esterified form, retinyl ester), mostly from animal sources or as a pro-vitamin A carotenoids, beta-carotene, alpha-carotene, and beta -crypto-xanthene, mostly from plant sources. The body converts these plant pigments into vitamin A. Both provitamin A and preformed vitamin A must be metabolized intracellularly to retinal and retinoic acid; the active forms of vitamin A to support its important biological functions[(9)] .

It is involved in immunological response, vision, reproduction, and cellular transport. It also supports cell growth and differentiation by playing a critical role in the normal formation and maintenance of the heart, lungs, kidneys, and other organs. Moreover, It plays an important role in nervous system development and neuronal regeneration[(10)] .

Retinol-binding protein 4 (RBP4) is only specific carrier protein of retinol in circulating blood and its concentration is directly proportional to the serum level of retinol [(11)]. Although RBP4 is synthesized mainly in hepatocytes, adipose tissue is also considered an important source of circulating RBP4 [(12)]. In Germany, a previous cohort study showed serum RBP4 concentration was inversely associated with the risk and prognosis of ALS [(13)].

AIM OF THE WORK:

This study aimed to measure the serum level of retinol-binding protein 4 (RBP4) in ALS patients in comparison to age and sex-matched healthy controls and to investigate the relation between the clinical aspects of ALS and serum retinol-binding protein 4 (RBP4) concentration as a biomarker for vitamin A metabolism in ALS patients.

SUBJECTS AND METHODS:

This is a case-control study performed in the neuromuscular unit, Neurology Department, Ain-Shams University hospital. The study period was one year. During this period 40 ALS patients were recruited from the neuromuscular unit in the outpatient clinic, Neurology Department, and matched with 40 healthy controls of matched age and sex, who exhibited no symptoms or family history of neuropsychiatric disorders or diabetes.

Inclusion Criteria:

- Patients diagnosed with ALS based on electrophysiological and clinical criteria according to Revised El Escorial criteria [(14)] to exclude ALS mimics

Exclusion Criteria:

- Patients suffering from ALS- mimics (not fulfilling diagnostic criteria and other differential diagnosis criteria)

- ALS patients suffering from diabetes type 1 and 2

Control Group:

Forty control subjects were selected and matched based on age and sex with patients. They must not have any personal or family history of neuropsychiatric disorders or diabetes and went through detailed neurological examination and cognitive assessment.

Ethical Consideration:

Written informed consent was obtained from each participant after explaining the aim of the study and all the procedures that were done. Privacy & confidentiality were considered. This study took place after the approval of the Research Ethics Committee, Faculty of Medicine, Ain Shams University.

Methodology:

All patients were subjected to:

Clinical assessment:

- Detailed recording of history including clinical data, demographic data, detailed family history, history of past illness, and detailed history of present illness (age of onset, site of onset, symptom progression, etc…)
- Detailed clinical examination, particularly neurological examination, including motor and cognitive function
- Determination of ALS clinical phenotype
- Revised ALS functional staging scale[15]
- Fronto-temporal dementia (FTD) diagnosis based on cognitive assessment.

Laboratory investigation:

- Venous blood samples were collected from both groups. Three ml were collected in a vacutainer (red capped) and samples were allowed to clot for 30 minutes at room temperature before centrifugation for 15 minutes at 1000 x g. Serum was removed and aliquoted and stored at -80 degree celcuis till analysis
- Quantitative determination of human retinol-binding protein 4 concentrations in serum was assayed by **Quantikine ELISA kit** [16]

The Quantikine® Human RBP4 immunoassay is a 2.5-hour solid-phase ELISA designed to measure human RBP4 in cell culture super nates serum, plasma, urine, and saliva. It contains NS0-expressed recombinant human RBP4 and has been shown to accurately quantitate the recombinant factor. Results obtained using natural human RBP4 showed linear curves that were parallel to the standard curves obtained using the Quantikine® kit standards. These results indicate that this kit can be used to determine relative mass values for natural human RBP4. Analytical sensitivity 0.628 ng/ml.

Calculations of the results were obtained by plotting the Standards of optical density against their known concentration on a linear curve. Patients' readings were interpolated and their concentrations were recorded.

Statistical analysis:

The collected data were coded, tabulated, and statistically analysed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 28.0, IBM Corp., Chicago, USA, 2021. Quantitative data tested for normality using Shapiro-Wilk test, then if normally distributed described as mean ± SD (standard deviation) as well as minimum and maximum of the range, then compared using independent t-test (two independent groups) and ANOVA test (three independent groups), while Pearson test was used for correlations. Qualitative data was described as numbers and percentages and compared using Chi-square test and Fisher's Exact test for variables with small expected

numbers. The level of significance taken at P value < 0.050 was significant, otherwise was non-significant.

RESULTS:

This study included 40 ALS patients with a median age of 41.5 years old, male percentage was (82.5%) and 40 matched controls with a median age of 43 years old, male percentage was (82.5%). There is no statistically significant difference between the 2 groups regarding demographic data or risk factors i.e.: hypertension and smoking (Table 1).

Table (1): Demographic characteristics and risk factors among the studied groups.

Items	Measures	ALS (N=40)	Control (N=40)	P-value	Significance
Age (years)	Mean ±SD	44.4±13.1	45.8±13.5	^0.634	NS
	Median (1st−3rd IQ)	41.5 (34.3−57.0)	43.0 (34.8−58.0)		
	Range	13.0–66.0	13.0–68.0		
Sex (n, %)	Male	33 (82.5%)	33 (82.5%)	#0.999	NS
	Female	7 (17.5%)	7 (17.5%)		
Smoking		20 (50.0%)	19 (47.5%)	#0.823	NS
Hypertension		4 (10.0%)	5 (12.5%)	§0.999	NS

IQ: Interquartile. ^Independent t-test, #Chi square test. §Fisher's Exact test, S = Significant, NS=non-significant.

The most common risk factors among the ALS group were consanguineous marriage and positive family history (30%), and (27.5%) respectively. Risk factors among the ALS group is shown in table 2.

Table (2): Risk factors among the ALS group.

Risk factors	n(total=40)	%
Consanguinity	12	30.0
Family history	11	27.5
Pesticide exposure	3	7.5
Head trauma	3	7.5

n=number

RBP4 serum level was statistically non significantly higher among the control group; (p - value >0.05) versus the patients' group (Table 3).

Table (3): Serum RBP4 (mg/L) among the studied groups

Measures	ALS (n=40)	Control (n=40)	^p-value
Mean ± SD	97.8±49.2	116.0±55.3	0.122
Range	15.0–190.0	30.0–240.0	
Median (1st−3rd IQ)	95.0 (60.0–130)	112.0 (70.0–167.5)	

^Independent t-test.

Serum RBP4 among the ALS group showed no statistically significant difference considering sex, smoking, or hypertension (p>0.05) but was statistically significantly higher in cases with positive family history (p<0.05) (Table 4).

Table (4): Correlation between serum RBP4 (mg/L) and the demographic characteristics and risk factors among the ALS group

Characteristics		n	Mean ± SD	p-value	Significance
Sex	Male	33	99.6±52.2	^0.605	NS
	Female	7	88.9±33.4		
Smoking	Present	20	109.8±52.8	^0.125	NS
	Absent	20	85.8±43.3		
Hypertension	Present	4	101.3±63.3	^0.883	NS
	Absent	36	97.4±48.5		
Consanguinity	Positive	12	99.4±46.4	^0.891	NS
	Negative	28	97.0±51.2		
Family history	Positive	11	136.4±36.1	^0.001*	S
	Negative	29	83.1±45.8		
Pesticide exposure	Positive	3	125.0±26.0	^0.325	NS
	Negative	37	95.5±50.2		
Head trauma	Positive	3	120.0±17.3	^0.423	NS
	Negative	37	95.9±50.6		

^Independent t-test, n=number, S=Significant, NS= non-significant

Serum RBP4 level was statistically significantly higher in cases that received nasogastric intubation showing a p-value <0.05. Medications intake showed no statistically significant difference in serum RBP4 level (Table 5).

Table (5): Correlation between serum RBP4 (mg/L) and management among ALS group

Characteristics		**n**	**Mean ± SD**	**p-value**	**Significance**
Nasogastric intubation	**Present**	6	141.7±33.3	**^0.016***	**S**
	Absent	34	90.0±47.8		
Medications (none)	**Present**	16	106.7±50.5	^0.355	NS
	Absent	24	91.8±48.5		
Medications (Riluzole)	**Present**	23	94.5±47.7	^0.631	NS
	Absent	17	102.2±52.3		
Medications (Edaravone)	**Present**	3	58.3±27.5	^0.152	NS
	Absent	37	100.9±49.4		

^Independent t-test, n=number, S=Significant, NS= non-significant

No significant correlation between serum RBP4 and age, age of onset, duration of illness, and ALS-FRS score among the ALS group (Table 6).

Table (6): Correlation between serum RBP4 and some clinical characteristics among the ALS group

Characteristics	r	p-value	Significance
Age	0.118	0.467	NS
Age of onset	0.065	0.689	NS
Duration of illness	0.179	0.270	NS
ALS FRS score	-0.015	0.928	NS

Total=40. r= Pearson correlation, NS=non-significant

DISCUSSION:

The current study aimed to measure the serum level of retinol-binding protein4 (RBP4) and to investigate the association between the clinical aspects of ALS and serum retinol-binding protein 4 (RBP4) concentration as a potential biomarker for vitamin A metabolism in ALS patients.

RBP4 is the only known carrier protein for retinol in the circulating human blood[17] therefore, it is a validated surrogate marker for serum retinol [18 &19]. In 2019, a study proved that there is a direct significant association between RBP4 levels and vitamin A intake. According to this finding, higher vitamin A intake could elevate the expression of RBP4 probably due to the demand for transportation and metabolizing of this vitamin [20]. Also, the vitamin A derivatives all-trans retinoic acid (atRA) and 9-cis RA were found to be potent inducers of RBP4 gene expression in vitro and in vivo (murine liver)[21]. Another study examined the effects of atRA treatment, it ascertained that atRA lowered mRNA expression of RBP 4 gene in adipose tissue but not in the liver, while repressing hepatic RBP4 protein and inducing serum RBP4 levels[22].

Vitamin A as a fat-soluble vitamin plays a vital role in proper brain and nervous system development and neurite regeneration [23] Several studies have proven that there is a correlation between fruits and vegetable intake as a source of antioxidants and beta carotene and ALS occurrence and progression[24&25]. Moreover, in 2014 a study showed that fruits and vegetable intake was negatively associated with the risk of ALS[26]. Moreover, as the precursor of retinol and retinoic acid several researches, including genetic, histopathological, and experimental studies, support the concept that retinoids play an important role in ALS pathogenesis[27,28&29].

Retinoic acid is proven to have a crucial role in cellular differentiation, programmed cell death, and other vital cellular function[30&31]. Regarding the nervous system, retinoids seem to be essential in the induction of neural differentiation, motor axon outgrowth and neural patterning. In line with this, Retinoids modulate the expression of hundreds of genes, including a large number of neuronal genes[32&33]. In addition, recent investigations suggest that retinoids could contribute to protein metabolism modulation affecting cellular proteostasis. From this perspective, Cheng et al.[7] showed that ATRA/RA treatment had a neuroprotective effect in cultured neuroblastoma cells under conditions of proteasome inhibition.

In accordance with this, retinoid-regulated neuronal genes might impact other important cellular processes, such as the antioxidant response (SOD1), neuro-inflammation and immune modulation, cytoskeletal organization (neurofilament L, M, H proteins), ion transport (K+ channel, Ca++ channels), intracellular signaling and synaptic homeostasis[29&33].

In early research, dietary retinoic acid supplementation increased symptoms in an ALS mouse model [34]. However, more recent research using high-affinity retinoid agonists in the same mouse model revealed a protective effect suggesting that retinol metabolites might be ALS modulator [5]. The current study supports this idea and further research is needed in this field.

The present study is a case-control study on 80 subjects (40 ALS patients and 40 matched age and sex healthy controls). The ALS patients were recruited from the neuro-muscular unit, Neurology Department in Ain Shams University hospital. ALS patients' diagnosis in the present

study was based on electrophysiological and clinical criteria according to the Revised El Escorial criteria [(14)] to exclude ALS mimics. The control subjects were randomly selected from the general population and underwent detailed neurological examination and cognitive assessment exhibiting no personal or family history of neuropsychiatric disorders or diabetes.

Excluding diabetes was based upon the fact that RBP4 is an adipokine with potential involvement in the pathogenesis of insulin resistance and diabetes mellitus[(35,36&37)] .

In the current study, the median serum level of RBP4 in ALS patients was lower than its level in the control group (95 vs 112 mg/L). This relation was of no statistically significant difference (p-value 0.122). **Rosenbohlem et al.** [(13)] found that the median serum RBP4 concentration was statistically significantly lower in ALS cases than in controls (54.0 vs 59.5 mg/L). This might be due to the difference between the sample sizes of the studies as the German study recruited 289 patients and 504 controls. Ethnicity might also have played a role, an American study based on the national ALS registry revealed that the prevalence of European-American ALS patients was found to be doubled that of African- Americans ALS patients (5.4 versus 2.3 per 100,000)**[(38)].**

The present study revealed no statistically significant difference between the two studied groups regarding demographic characteristics.

Regarding the clinical characteristics among the ALS group in the current study, the classical phenotype was found to be the most frequent phenotype, representing 77.5 % of the patients. Moreover, it was found that weakness was the most frequent clinical presentation 67.5%, while dysphagia and dysarthria accounted for 15% and 7.5 % respectively. These findings are in accordance with **Štětkářová and Ehler (2021)[(39)].**

Among ALS patients, consanguineous marriage accounted for 30% and positive family history accounted for 27.5% respectively, although familial ALS accounts for 5-10% only of ALS patients[(40)].

No significant statistical difference in serum RBP4 levels among ALS patients regarding age, age of onset or duration of the disease[(41)].

Considering the correlation between serum RBP4 level (mg/L) and sexual predominance there was no statistically significant difference as sex has no influence on RBP4 serum levels[(42)].

Although several studies had shown that serum RBP4 levels were significantly elevated in patients with untreated essential hypertension and associated with elevated systolic and diastolic blood pressure in prehypertensive patients [(43&44)] yet the current study revealed no statistically significant difference in serum RBP4 levels of hypertensive ALS patients.

The present study also showed no statistically significant difference in RBP4 serum levels among smokers in ALS patients' group although several studies proved that smoking is correlated to RBP4 levels concentration in blood[(45,46&47).]

Serum RBP4 was found to be statistically significantly higher in cases with a positive family history (mean value136.4±36.1) versus cases with a negative family history (83.1±45.8) which may highlight that there is a hereditary factor for RBP4 serum level in blood which might be due to the RBP4 gene transcription regulation by multi-complex proteins [(48)].

In addition, the present study revealed that cases that underwent nasogastric intubation have had statistically significant high levels of RBP4, most probably due to the nutritional intervention with a well-balanced diet **(24).** It is believed that nutritional care plays an important role in ALS pathogenesis and progression focusing on high anti-oxidant sources and carotenes improves ALS function and quality of life**(49).** Moreover, **Welles et al.,2021** proved that the translation of Rbp4 mRNA was increased upon acute re-feeding of fasted rodents**(50).**

Conclusion:

Serum RBP4 concentration was found to be lower in ALS patients than in the controls group although statistically nonsignificant, implying that RPB4 serum level concentration may be linked to ALS pathogenesis. To fully understand the relation between ALS occurrence and vitamin A metabolism, more studies are required to delineate the effects of vitamin A on the onset and prognosis of ALS, including prospective design studies and investigating other retinoid metabolites.

Conflicts of Interest: The authors state that the publishing of this paper is free of any conflicts of interest.

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مستوى البروتين الملزم للريتينول ٤ في المصل و علاقته بتصلب اللوحي الضموري بين المرضي المصريين

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[٣] قسم المخ والأعصاب بكلية الطب-جامعة عين شمس
[٤] قسم علم الأدوية والسموم بكلية الصيدلة والتكنولوجيا الحيوية الجامعة الألمانية بالقاهرة

المقدمة: التصلب الجانبي الضموري هو مرض تنكسي عصبي يؤدي الي شلل تدريجي يتسبب في تنكس العصب الحركي العلوي والسفلي، ولا يصيب عضلات العين الخارجيه والعضلات العاصرة القابضة، سبب المرض وعوامل الخطر لا تزال غير مفهومة بالكامل، في الآونة الأخيرة، تشوهات التمثيل الغذائي والعوامل الغذائية أصبحت هي محور الاهتمام. أظهرت العديد من الدراسات أن هناك علاقة، بشكل مباشر أو غير مباشر، بين ALS وحمض الريتينويك وهو عامل مهم لتطور الخلايا العصبية الحركية وتحفيز تجديد العصبي في الأعصاب الطرفيه.يعتبر فيتامين (أ) هو السلاف لحمض الريتينويك ويعتبر البروتين المُلزم للريتينول ٤ هو الملزم الوحيد لحمض الريتينويك في الجسم.

الهدف من البحث: قياس مستوى البروتين الملزم للريتينول ٤ في مصل الدم لدى مرضى الضمور اللوحي التصلبي مقارنة بالضوابط الأصحاء المتطابقة مع الجنس والنوع وربط مستويات البروتين الملزم للريتينول ٤ بالجوانب السريرية للمرض ودراسة امكانيه استخدامه كمؤشر حيوي لمرض التصلب اللوحي الضموري.

الأشخاص والأساليب المستخدمة: هذه دراسة حالة وضبط تم إجراؤها على ٤٠ مريضًا بمرض التصلب الجانبي الضموري تم تجنيدهم من الوحدة العصبية والعضلية في قسم الأعصاب بمستشفى الدمرداش و٤٠ عنصر تحكم متطابق في العمر والجنس وأصحاء تم اختيارهم عشوائيًا من المجتمع.

تمت هذه الدراسة بعد موافقة لجنة أخلاقيات البحث العلمى بكلية الطب جامعة عين شمس. وتم جمع عينات ٣ مللى من الدم الوريدي من كلا المجموعتين الضابطة والمرضى وتمت إزالة المصل وتقسيمه وتخزينه عند درجة مئوية -٨٠ مئوية حتى التحليل. تم تقييم التحديد الكمي لتركيزات بروتين رابط الريتينول البشري ٤ في المصل باستخدام تقنية

Quantikine ELISA (2017 R & D Systems ،inc.)

تم ترميز البيانات التي تم جمعها وجدولتها وتحليلها إحصائيًا باستخدام إصدار برنامج IBM SPSS (الحزمة الإحصائية للعلوم الاجتماعية) ٢٨،٠ .IBM Corp، شيكاغو، الولايات المتحدة الأمريكية ٢٠٢١.

النتائج: أظهرت نتائج البحث أن مستوي البروتين الملزم للريتينول ٤ في المصل لم يكن عاليا بصورة ملحوظة احصائياً في مصل الضوابط عنه في مصل مرضي الضمور اللوحي التصلبي.

الخاتمة: بالرغم أن مستوي البروتين الملزم للريتينول ٤ في المصل لم يكن عالياً بصورة ملحوظة احصائياً في المجموعة الضابطة الا أنه قد يشير إلى أن الألية الحيوية المنظمة لتركيز البروتين الملزم للريتينول ٤ لها علاقه بطريقه تطور مرض الضمور اللوحي التصلبي.