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Enzymatic Study of Methionine Sulfoxide Reductase A, some other Enzymes Associated with Neural Pathways and Oxidative Stress in Down Syndrome Patients in Mosul City

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ABSTRACT

Down syndrome (DS) is a genetic disorder that arises when a third chromosome 21 is found in either some or all cells of the body contributing to complex conditions involving intellectual disability and learning inability. Oxidative stress (OS) has been correlated, which plays an important role in rapid aging, how antioxidants utilize in treating cognitive defect, oxidative damage of biomolecules in DS, also disruption of some neurotransmitter levels in the neurons has been observed. This study was conducted to measure in serum of (50) DS individuals against (25) of control group, Methionine Sulfoxide Reductase (MsrA), Senescence Marker Protein-30(SMP-30), Thioredoxin (TRX), glutamate decarboxylase 67 (GAD67), Serotonin N-acetyltransferase (AANAT), Catechol O-Methyl Transferase (COMT), Methionine S-Adenosyl Transferase (MAT), monoamine oxidase A (MAOA) in addition to peroxynitrite (ONOO–) and malondialdehyde (MDA). Decreased levels of the activity of MsrA, SMP-30 was observed while GAD67, AANAT, TRX and peroxynitrite show significantly higher levels in DS comparing with control group. There is no alteration COMT, MAT, MAOA and MDA. Significant positive correlation between MsrA, peroxynitrite and MAT, without relation with GAD67, AANAT in which (ONOO–) may trigger MsrA that will provide the substrate for MAT. Therefor the higher oxidative stress, represented by lower antioxidants activities related to senescence, may indicate acceleration of aging in patients. Additionally, elevation of TRX may indicate oxidative damage to macromolecules. γ-Aminobutyric acid (GABA) neuron and N-acetyl-serotonin may be affected by the higher concentration of GAD67 and AANAT, respectively.

Keywords: Methionine sulfoxide reductase, oxidative stress, down syndrome, neurotransmitters, antioxidants.

INTRODUCTION

Live-born children may develop Down Syndrome (DS) as they have additional chromosome 21 present in either whole or partial form in some or all cells of the body (Akhtar and Bokhari, 2024). The primary distinction is intellectual disability, but there are also other common characteristics such as congenital heart disease, Alzheimer's disease, leukemia, abortion, hypotonia, motor disorders, learning inability, variation in intelligence quotient, attention and memory (Al-Helaly and Mahmood, 2019; Micangeli *et al*., 2022; Al-Hamdani and Al-Helaly, a2023). Many of these symptoms are believed to be linked to enhanced oxidative stress (Wernio *et al*., 2022), also during life, oxidative damage accumulates in brain of individuals with DS, resulting in neurodevelopmental impairment, neuronal dysfunction, and a faster aging phenotype (Antonarakis *et al*., 2020; Perluigi *et al*., 2022). Increase levels of oxidants, lead to modification of proteins and genes are related to mitochondria and others (Perluigi *et al*., 2020; Hameed and Al-Helaly, 2020). Superoxide dismutase (SOD-1) in various tissues, especially the brain, was affected by the triplication, this resulted in the overproduction of hydrogen peroxide, leading to its accumulation due to disproportionate levels of the metabolic enzymes catalases (CAT) and glutathione peroxidase (GPx). Besides elevated levels of ROS promote oxidative damage of macromolecules and amino acids (For example methionine) (Oien *et al*., 2010). Oxidation of free methionine or methionine residues in proteins provides antioxidant defines when there is methionine sulfoxide reductase type MsrA or MsrB, by reacting with oxidizing species, which oxidize methionine to methionine sulfoxide with two epimers, while this is a crucial reaction that has a significant impact on protein modifications during oxidative stress and aging that involving decline levels of MsrA (Vinokur *et al*., 2009; Marciniak and Bobrowski, 2022; Al-Hamdani and Al-Helaly, b2023). It is specialized for the reduction of free and protein-based methionine-S-sulfoxide in mammals back to methionine (Chandran and Binninger, 2023).

The level of MsrA correlates with the removal of accumulated oxidative damage, as demonstrated by several studies (Lee *et al*., 2006; Garrett and Grisham, 2024). MsrA system may also play an important role in specific disease processes: Schizophrenia (SCZ), Alzheimer's disease (AD), and Parkinson's disease (PD) as well as metabolic disorders including obesity and diabetes share a common thread of Msr dysfunction (Chandran and Binninger, 2023). Studies involving wild type mice have shown that aging, regardless of any disease, causes a diminish in MsrA activity, also its mRNA is in decreased level (Vinokur *et al*., 2009).

Furthermore, the enzymes that involved in neurotransmission was also included in this study (in statistic correlation to MsrA). DS has resulted in GABAergic defects that affect learning, cognitive impairment, and significant changes in the levels of noradrenaline, choline acetyltransferase, and serotonin in almost all cortical and subcortical tissue regions (Deidda *et al*., 2014). The dopamine levels in the brain and cerebrospinal fluid of DS patients have been reported to be elevated and decreased from those in healthy people (Whittle *et al*., 2007).

According to that situation related to MsrA, we introduce it as indicator of oxidative damage of biomolecules (Free Met and proteins especially that are included in neurotransmission pathways) in addition to senescence marker protein-30 (SMP-30) to determine if individuals with DS suffer from rapid aging, the cells act like elderly cells, or they appear like those in AD or PD.

METHODS

The research parameters were measured in the blood serum of patients' groups (n=50) with different ages of (5-26 years) against the same range of (n=25) control group. Al-Salam teaching hospital, Ibn Sina teaching hospital, in addition to private special needs schools in Mosul city were responsible for blood collection of DS individuals, while Central Blood Bank and schools are for normal persons during November and December 2023. The blood serum separation was accomplished by transferring the blood samples into gel tubes and centrifuged at 3000 g for 10 minutes after leaving them for 10 minutes at room temperature. The serum was separated and used

for tests of biochemical markers which were conducted in the laboratories of the College of Science/ University of Mosul.

ELK Biotechnology's ELISA kit was used to determination of GAD67 (ELK3676), AANAT (ELK5237), and COMT (ELK3245). MsrA was measured by using Ellman's reagent in the presence of dimethyl sulphoxide (DMSO) as substrate, Dithiothreitol (DTT) acts as thioredoxin for reduction of MsrA due to its structure that includes two groups of (SH). 5,5`dithio bis (2-nitrobenzoic acid) (DTNB) easily reacts with oxidized DTT that equals to enzyme concentration to give yellow color that detected at 412nm (Wu *et al*., 2013; Das *et al*., 2020). Green malachite-molybdate solution that is used in determination of inorganic phosphate was applied to measured MAT (in the presence of ATP that will provide phosphate group to the product) catalyzes the formation of s-adenosyl methionine from methionine as a substrate. At the end of the reaction, the product Pyrophosphate can be detected by green malachite at 620nm (Yin *et al*., 2017). The method of reducing the disulfide bridge of insulin was used for determination of thioredoxin, Insulin consists of two peptide chains connected by two disulfide bridges that can be reduced by thioredoxin catalytic activity in the presence of DTT, turbid solution is formed due to free B chain can be detected at 650 nm (Holmgren, 1979), while the modified technique for measuring $ONOO^-$ of Vanuffelene *et al*. in 1998 was used. The thiobarbituric acid (TBA) technique was employed to determine MDA serum levels (Muslih *et al*., 2002), while, P-nitrophenol was used in the method to determine, SMP-30, acts as gluconolactonase for converting gluconolactone to D-gluconate, Hydrolysis of D-glucono-lactone will decrease the absorbance of p-nitrophenol by increase the acidity of solution (Hucho and Wallenfels, 1972). MAOA was measured by its activity for oxidative deamination of benzylamine to benzaldeyde that can be detected at 250nm (Buffoni and Blaschko, 1964).

Statistical analysis:

The data was presented using the mean and standard errors (SE) after statistical analysis using the t-test. When P-values were ≤ 0.05, a significant variation was taken into account (Mansournia *et al*., 2021; Faizi and Alvi, 2023).

RESULTS AND DISCUSSION

As shown in (Table 1), the serum antioxidants levels of DS were in an alteration compared with control group. MsrA and SMP-30 were decreased significantly (372.99±33.301) and (0.210±0.025) compared with control group (485.13±38.05) and (0.326±0.035) respectively. While TRX was increased in DS (331.19±65.83) compared with (102.40±29.21). The levels of oxidants were influenced significantly by ONOO- in DS individuals (42.61±4.14), compared with control group (24.83±4.07) but it is not observed in MDA.

Table 1: Mean ±S.E. of antioxidants and oxidants levels in Down syndrome patients compared with control groups.

Biochemical parameters	Control group		Down syndrome group		P value
	Mean	S.E.	Mean	S.E.	
MsrA(U/L)	485.13	38.05	372.99	33.301	0.032*
TRX(U/L)	102.40	29.21	331.19	65.83	0.048*
SMP-30(U/L)	0.326	0.035	0.210	0.025	0.034*
$ONOO^-$(µmol/L)	24.83	4.07	42.61	4.14	0.003*
MDA(µmol/L)	2.116	0.099	2.248	0.160	0.656

*Significant at ($P \leq 0.05$).

Peroxynitrite in its elevated level in DS patients group causes oxidative stress, this suggests oxidative damage to molecules in different cells. In relation with methionine residues, ONOO- is able to oxidize, resulting in methionine sulfoxide (MetO) formation (Garrett and Grisham, 2024). In response to this situation, the antioxidant system was expected to activate MsrA. Normal cellular level of MsrA with normal activity made the reduction of MetO was very efficient for reduce $ONOO^-$, hydrogen peroxide induced-oxidative damage (Tarrago *et al*., 2020; Hameed and Al-Helaly, 2021).

Decreased activity of MsrA that we found in DS refers to many considerations: Accumulation of MetO that may effect on the methionine metabolism in the brain and liver especially in producing S-Adenosylmethionine (SAM) that represents a key of methylation process of DNA and neurotransmitters, also producing the important antioxidant peptide (Glutathione), after tested the activity of methionine adenosyltransferase in the serum, the result shows that the patients had very close activity to the control group, so this reflect that SAM was in normal level to do its function. The statistic correlation shows significant positive linear relationship between MsrA and MAT, this suggest that methyl donor molecule was influenced by the lower activity of MsrA then results in change in methylation that related to neurotransmission and the normal level of MAT may related to the high methionine diet (Wang *et al*., 2019). Peroxynitrite shows significant positive relation with MsrA and MAT that it is not expected if assume that peroxynitrite cause methionine residues oxidation of MAT but this may indicate to the role of MsrA that is activated by higher level of $ONOO^-$ and provide a substrate for MAT.

Several researches for SMP-30 knockout mice demonstrated its role as antioxidant in neurons, antiapoptosis and insufficient SMP30 increases neuroinflammation and anxiety-like behavior, this suggests that the patients may showed rapid aging. Different studies demonstrated that MsrA overproduction prevents oxidative damage caused by H_2O_2 in eukaryotic species in general, and in cellular level, lens cells and fibroblast cells. This suggests that decreased activity that we found may enhance oxidized protein accumulation (Liu *et al*., 2021; Baek *et al*., 2021).

As shown in (Table 2), GAD67, AANAT are significantly increased in DS group (1.57±0.523) and (4.139±0.446) compared with control group (0.43±0.073) and (3.47±0.416), respectively, with no significant alteration in COMT, MAT and MAOA.

Table 2: Mean ± S.D. of some enzymes in Down syndrome patients compared with control groups.

Biochemical parameters	Control group		Down syndrome group		P value
	Mean	S.E.	Mean	S.E.	
GAD67 (ng/ml)	0.43	0.073	1.57	0.523	0.035*
COMT (ng/ml)	3.55	0.460	3.331	0.337	0.954
AANAT (ng/ml)	3.47	0.416	4.139	0.446	0.048*
MAT (U/L)	52.67	5.58	51.99	5.91	0.804
MAOA (U/L)	631.44	35.58	651.26	36.56	0.609

*Significant at ($P \leq 0.05$).

Accumulation of oxidized methionine residues that cause modifications to enzymes or proteins results in loss of function. In connection with this, neuronal proteins were significantly damaged compared to postmortem brains of Alzheimer's disease patients and aging rats due to decreased MsrA activity (Gabbita *et al*., 1999). So, three parameters were chosen: GAD67, AANAT and COMT as a causative of the implication of the neurotransmission that related to cognitive as reported by researches, also they have an abundance of methionine residues in order to investigate the statistical relation with MsrA on the assumption that it is repair enzyme. The three enzymes observed had no correlation with MsrA, in which GAD67 and AANAT showed higher levels compared to the control group, although evidence showed that several proteins were substrates for Msr during the study the

effects of Msr mutation (Cabreiro *et al*., 2009). More research is required to investigate the level of MetO in neural enzymes and evaluate the role of MsrA, particularly there is study mention that Met oxidation may also promote protein activity (Drazic and Winter, 2014).

Insufficient level of thioredoxin that is considered the reducing agent of MsrA in the presence of thioredoxin reductase/NADPH was predicatded due to decreased activity of MsrA but after investigation the serum concentration of, it has been elevated in DS, this may suggest that thioredoxin system is not implicated in the MsrA dysfunction but it gives a sign that there is oxidative damage to molecules (Hamdon and Al-Helaly, 2019).

Oxidative stress caused by hydrogen peroxide was observed enhances premature senescence in human and mouse cells and as reported by several studies, Aging causes a decrease in MsrA activity, regardless of any illness, as shown in studies with WT mice. This decrease in the activity correlates with decreased MsrA mRNA levels (Vinokur *et al*., 2009). We utilize the activity of this enzyme as an indicator for aging, side by side with MsrA, determination of SMP-30 was conducted in order give a sign about aging, especially since DS individuals show accelerating aging according to (Lott and Head, 2019). The cells may act as senescent cells due to the loss of antioxidant activities and lower production of MsrA and SMP-30.

In the other hand, GABA and melatonin synthesis may be disrupted by a higher level of GAD67 and AANAT, respectively. Several reasons related to higher GAD67, glutamate concentration within neuron was higher and it is known that causes toxicity for neurons also destroying target neurons (Choi, 1994). The response of GAD67 to this condition makes it in elevated level at the same time, GABAergic dysfunction mentioned reduces cognitive, memory, and learning abilities in DS. It may be that it was declined, represented by increased GAD67, which may reflect the need for GABA basal production in neurons. Whereas studies show GABA level trigger GAD activity in order to respond to the change. Increased antioxidant activity by producing more glutathione was suggested through expression of GAD67 in astrocytes, then securing the neurons from damage (Lamigeon *et al*, 2001).

For study the cause of sleep problem in DS, as reported by Maris *et al*. (2016) and some studies explained that melatonin level is decreased in brain and plasma (Bakhsha, *et al*., 2019). AANAT higher level may represent the response to decreased level of melatonin especially AANAT is the rate limiting step in melatonin synthesis. Higher may also represent the responding for elevated serotonin notably that monoamine oxidase A was in normal level or (tryptophan metabolism) that has been disrupted in DS according several studies (Powers *et al*., 2019). Studies of melatonin showed its taking enhances spatial learning and memory, acts as an antioxidant and anti-aging in the hippocampus of adult mice. On the other hand, in MsrA knockout mice a gradual loss of personal communication occurred with some effects may be related to mental health disorders, this is confirmed with the alteration of GAD67 and AANAT in addition to MsrA.

CONCLUSIONS

According to the observed results, reduced activity of MsrA may result in accumulation of methionine sulfoxide within amino acid sequences in protein particularly in the brain that showed oxidative stress. Therefore, more studies are needed to ensure the influence of MsrA activity on rain proteins, it can be used later as a therapeutic target in the patients. It is important to investigate the correlation between SMP-30 and MsrA to determine if MsrA affects activity of SMP-30 ecause of the presence of methionine in its amino acid sequence. The elevated levels of thioredoxin could be a marker for the presence of oxidized protein within cells. Finally, GAD67 and AANAT may play a role in the alteration level of GABA and melatonin in DS, respectively.

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دراسة انزيمية لمثيونين سلفوكساید ردكتيز A وبعض الانزيمات الاخرى المتعلقة بالمسارات العصبية وحالة الكرب التأكسدي في مرضى متلازمة داون في مدينة الموصل

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الملخص

متلازمة داون (DS) هي اضطراب وراثي ينشأ عندما يتم العثور على كروموسوم ثالث 21 في بعض أو كل خلايا الجسم مما يساهم في حالات معقدة تنطوي على الإعاقة الذهنية وعدم القدرة على التعلم. تم ربط الإجهاد التأكسدي، والذي يلعب دورًا مهمًا في الشيخوخة السريعة، وكيفية استخدام مضادات الأكسدة في علاج الخلل الخلقي، والضرر التأكسدي للجزيئات الحيوية في مرضى متلازمة داون، كما لوحظ اضطراب في مستوى بعض النواقل العصبية في الخلايا العصبية. اجريت هذه الدراسة في مصل الدم لـ (50) فردًا من مرضى متلازمة داون مقابل (25) فردا كمجموعة سيطرة وقد تم قياس متغيرات كل من: إنزيم سلفوكساید ميثيونين ردكتيز A (MsrA) وبروتين علامة الشيخوخة-30 (SMP-30)، وثايوريدوكسين (Trx)، وكلوتاميت ديكاربوكسيليز 67 (GAD67)، وسيروتونين N–أسيتايل ترانسفيريز (AANAT)، وكاتيكول O–ميثيل ترانسفيريز (COMT)، وميثيونين إس–أدينوسيل ترانسفيريز (MAT)، وأوكسيديز أحادي الأمين A (MAOA) بالإضافة إلى بيروكسي نيتريت ($ONOO^-$) والمالونداياليديهايد (MDA). وقد لوحظ انخفاض مستويات فعالية انزيمي MsrA وSMP-30 بينما أظهرت كل من GAD67 وAANAT وTRX و-ONOO مستويات أعلى بكثير في مرضى متلازمة داون مقارنة مع مجموعة السيطرة. ولم يكن هناك أي تغيير معنوي انزيمات COMT، MAT، MAOA ومركب MDA. هناك علاقة إيجابية معنوية بين انزيم MsrA و$ONOO^-$ وانزيم MAT، ولا توجد علاقة مع انزيمات GAD67 وAANAT حيث قد يؤدي ($ONOO^-$) إلى تحفيز انزيم MsrA الذي سيوفر مادة الاساس لانزيم MAT. ولذلك فإن الإجهاد التأكسدي العالي، الناتج عن انخفاض مستويات مضادات الأكسدة المرتبطة بالشيخوخة، قد يؤدي إلى تسارع الشيخوخة لدى مرضى متلازمة داون. بالإضافة إلى ذلك، ان ارتفاع TRX قد يكون ناتج عن اصلاح زيادة الاكسدة في الجزيئات الكبيرة. وبالتالي قد يتأثر الناقل العصبي كاما– حامض امينو بيوتاريك (GABA) وسيروتونين N– أسيتايل بالتراكيز العالي لكل من إنزيمي GAD67 وAANAT، على التوالي.

الكلمات الدالة: ميثيونين سلفوكساید ردكتيز، الكرب التأكسدي، متلازمة داون، النواقل العصبية، مضادات الأكسدة.