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MMP-2, MMP-9, TNF-α Levels In Relation To Subtypes of Attention Deficit Hyperactivity Disorder

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Many authors have suggested the association between Attention Deficit Hyperactivity Disorder (ADHD) and inflammation through various mechanisms among which increased serum cytokines. 30 newly diagnosed ADHD children, aged 6-12 and of both sexes were collected from outpatient clinic, Psychiatry Department, Al Zahraa University Hospital and a matched control group of 30 children. They were subjected to Clinical assessment, Whechsler Intelligence Scale for children (WISC), Conners' Parent Rating Scale-Revised & serum MMP-2, MMP-9, TNF-α levels were determined. There was statistical significant difference between patient and control groups regarding MMP-2 level (648.50 ± 81.94 vs 344.13 ± 32.02), MMP-9 level (143.00±16.98 vs 102.90 ± 4.13) & TNF-α level (345 ± 7.1.vs 202 ± 22.3). Hyperactive/ impulsive subtype represented 16(53.3%), Inattentive subtype represented 6(20%), Combined subtype represented 8(26.7%) of the ADHD group. MMP-2, MMP-9, TNF-α levels were all higher among the Hyperactive/impulsive subtype, followed by the combined subtype then the Inattentive subtype with high statistical significant difference. A high statistical significant difference was found in all subscales of Conners' scale among the 3 subtypes of ADHD. A positive correlation was found between TNF-α level and age, whereas, a negative correlation exists between MMP-2, MMP-9, TNF-α level and IQ. In addition, correlation was found between MMP-2, MMP-9 levels and cognitive problems, TNF-α level and inattention. Our study illustrates the co-occurrence of inflammatory process and ADHD, but further studies on larger sample are needed.

Keywords: Attention Deficit Hyperactivity Disorder, MMP-2, MMP-9, TNF-α.

Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorder in childhood, it can persist into adolescence and adulthood, it is characterized by sustained symptoms of inattention and/or hyperactivity and impulsivity, based on symptoms, 3 presentations of ADHD can occur: Combined Presentation, Predominantly Inattentive Presentation,

and Predominantly Hyperactive/ Impulsive Presentation [1].

The incidence of ADHD shows large variability, it is estimated to range between 3 - 11% [2] & reached 20% in school aged children in USA [3] & 20.5% in Egypt [4]. ADHD symptoms lead to significant impact on the children's quality of life as shown by poor academic performance, low self-esteem and progressive social deterioration [5].

The exact pathogenesis of ADHD is not fully understood, but a growing body of evidence for the role of the immune process and inflammatory mechanisms has been hypothesized [6].

Many authors have suggested the association between ADHD and inflammation[7,8,9]. The inflammatory pathways are related to the pathophysiology of ADHD through various mechanisms, among which increased serum cytokines as indicated by several studies [10].

TNF-α is a proinflammatory cytokine, produced by macrophages and other cells such as B cells, T cells and activated monocytes in response to various stimuli [11], it is involved in controlling a broad variety of biological processes including the proliferation, differentiation, apoptosis of cells [12]. It has also been documented that TNF-α plays a key role in tryptophan metabolism and dopaminergic pathways which are also involved in ADHD [13]. Moreover, TNF-α is a potent stimulant for metalloproteinases expression in the brain through their release and activation [14].

Metalloproteinases (MMPs) are extracellular matrix (ECM)-degrading enzymes involved in inflammatory processes and remodeling of tissues [15, 16].Thus, metalloproteinases have a role in the production of brain injury through either their proteolytic activity on the ECM or, moreover, their ability to increase the levels of soluble TNF-α levels as well [17].

Although many studies have investigated prevalence, characteristics and pathogenesis of ADHD patients, yet , no sufficient informations are available for evaluation of MMP-2, MMP-9, TNF-α in such patients.

Aim

Since the detection of ADHD pathogenesis is essential for the development of new therapeutic approaches, we aimed to measure serum matrix MMP-2, MMP-9 and TNF-α in ADHD and correlate them with subtypes of ADHD.

SUBJECTS AND METHODS

A case control study was conducted on a convenience sample of 30 newly diagnosed children with ADHD based on DSM 5 criteria, aged between 6- 12 and of both sexes, they were collected from outpatient clinic, Psychiatry Department, Al Zahraa University Hospital, Cairo, Egypt. Patients with other comorbid psychiatric, neurological, autoimmune disorders or intellectual disability or having history of infectious disease within the last 3 months were excluded from the study. A control group of 30 children matched for age and sex were recruited from typically developing children having no history of psychiatric, neurological, autoimmune disorders or intellectual disability or infectious disease within the last 3 months.

All participants were subjected to the following:

1. Clinical assessment with a semistructured psychiatric sheet based on psychiatric interview for children.
2. Whechsler Intelligence Scale for children (WISC) [18], Arabic version [19]: To assess different categories of IQ. Children with IQ < 70 were excluded from the study.
3. Conners' Parent Rating Scale-Revised [20], The Arabic version[21]: To diagnose ADHD in children and adolescents (3-18 years old), it comprises of 5 subscales: Cognitive problems, hyperactivity, inattention, liability and Hyperactivity/impulsivity.
4. Determination of serum MMP-2, MMP-9, TNF-α levels with the use of Enzyme-Linked Immunosorbent Assay (ELISA):

The human serum MMP-2, MMP-9 and TNF-α were assessed by using the RayBio ® Human ELISA (Enzyme-Linked Immunosorbent Assay). Instructions were followed for obtaining results. Samples were pipetted with MMP-2, MMP-9 and TNF-α human antibodies, they were incubated & then washed and biotinylated antihuman MMP-2, MMP-9 and TNF-α antibody were added. Biotinylated antibody and horseradish peroxidase-conjugated streptavidin were pipetted and washed again. Tetramethylbenzidine substrate solution was added & intensity of the developed color was measured.

Data analysis

Statistical analysis was performed using SPSS (Statistical Package of Social Science) version 21.0 for the collected and coded data. Statistical significant difference were considered at P value < 0.05.

RESULTS

The sociodemographic analysis of both ADHD and control groups showed that they were matching regarding age, sex, IQ assessment with no significant difference at P value. High statistical significant difference was present between both groups regarding MMP-2 level (648.50 ± 81.94, 344.13 ± 32.02 respectively), MMP-9 level (143.00 ± 16.98, 102.90 ± 4.13 respectively)&TNF-α level (345 ± 7.1, 202 ± 22.3 respectively).

ADHD group were further subdivided into 3 subtypes

Hyperactive/impulsive subtype representing 16(53.3%), Inattentive subtype representing 6(20%), Combined subtype representing 8(26.7%) of the patient group (Table 1).

Comparison between MMP-2 and MMP-9, TNF-α level in subtypes of ADHD shows that all levels were higher among the Hyperactive/ impulsive subtype, followed by the combined subtype then the Inattentive subtype with high statistical significant difference.

Comparing between subtypes of ADHD regarding WISC, no significant difference was found regarding total, verbal, performance IQ, however, a high statistical significant difference was present in all subscales of Conners' scale.

A positive correlation was found between TNF-α level and age, whereas, a negative correlation exists between MMP-2, MMP-9, TNF-α level and IQ. In addition, correlation was found between MMP-2, MMP-9 levels and cognitive problems, TNF-α level and inattention, Hyperactivity/impulsivity.

DISCUSSION

Recent studies have suggested the link between many psychiatric disorders and inflammatory processes such as schizophrenia and mood disorders [22]. Despite hundreds of studies conducted on ADHD, yet, its pathogenesis remains a controversial issue among researchers & the contribution of inflammation is still unclear. The exact role of MMP-2 in ADHD remains ambiguous due to lack of data in various studies, however, few studies are available on the relation between MMP-9, TNF-α and ADHD but none of them was conducted in Egypt. So, it seems necessary to us to

Table 1. Comparison between patient and control group regarding various parameters, MMP-2, MMP-9 and TNF-α levels

	Patient group (N=30)	Control group (N=30)	t test	P value
Age(mean ± SD)	9.37 ± 1.88	9.20 ± 1.75	t = 0.3625	0.7183
Sex				
Male	19	18	X^2=0.07	0.79
Female	11	12		
WISC(mean ± SD)				
Total IQ	96.80 ± 3.24	97.80 ± 1.75	t = 1.4874	0.1423
Verbal IQ	96.00 ± 3.25	97.1 ± 2.03	t=1.5723	0.1213
Performance IQ	96.70 ± 2.37	97.70 ± 2.22	t = 1.6867	0.0970
MMP-2(pg/ml)(mean ± SD)	648.50±81.94	344.13±32.02	t = 18.9499	<0.0001
MMP-9(pg/ml)(mean ± SD)	143.00±16.98	102.90 ± 4.13	t=12.5686	<0.0001
TNF-α(pg/ml)(mean ± SD)	345 ± 7.1	202 ± 22.3	t =33.4677	<0.0001
ADHD subtype (N,%)				
Hyperactive/impulsive	16(53.3%)			
Inattentive	6(20%)			
Combined	8(26.7%)			

Table 2. Comparison between MMP-2 and MMP-9, TNF-α level in subtypes of ADHD

	Hyperactive /Impulsive (N=16)	Inattentive (N=6)	Combined (N=8)	F test	P value
MMP-2 (pg/ml)(mean ± SD)	157±15.38a	118.17±1.94b	133.07±14.24c	20.63	<0.0001
MMP-9 (pg/ml)(mean ± SD)	713.75±38.47a	571.17±8.61b	621.00±44.90c	39.13	<0.0001
TNF-α (pg/ml)(mean ± SD)	357±7.4a	341±1.6b	345± 2.3c	22.61	<0.0001

Same letter means non-significant difference, while different letter means high significant difference at (P <0.001).

carry out this study to explore the eventual role of MMP-2, MMP-9 and TNF-α as possible markers of ADHD.

In our study, WISC assessment of IQ in both ADHD group and control group was statistically non-significant. In many studies, intellectual ability of children with ADHD was investigated & discrepancies between results were obtained. Although, some studies revealed differences in cognitive variables between ADHD children compared with healthy ones, yet, many studies were in accordance with our study, amongest which the study of Naglieri et al. who examined the relation between WISC and the scores of Conners' Scale (parent form) and found non-significant correlation[23]. Also, kaplan et al. tested 63 ADHD children with WISC & found the majority of ADHD children to have the average range of scoring [24].

In our study, There was high statistical significant difference between ADHD group and control group regarding MMP-2, MMP-9 & TNF-α levels. Our result was in accordance with the study of Kadziela-Olech et al. who studied a group of 37 boys with ADHD and found the level of MMP-9 was associated significantly with symptoms of ADHD[25]. Another study done by Soltanifar et al. on 20 children aged between 2- 10 were diagnosed with ADHD revealed an increase in the level of TNF-α in these children than in the control group [26]. These findings indicate a correlation between the risk of ADHD occurrence and inflammatory process.

To the contrary to our study, Oades et al. detected no differences in serum TNF-α in 21 ADHD treatment-naïve patients compared to the control group, however, they found significant differences between 14 medicated children and the non-medicated ones[27]. A larger sample group is mandatory to reach a final conclusion.

In our study, we also correlated MMP-2, MMP-9 & TNF-α levels with subtypes of ADHD. The highest level were found among the Hyperactive/impulsive subtype. The same result was obtained by Kadziela-Olech et al. who found a correlation between serum MMP-9 and impulsivity[25]. Also, Cortese et al. assessed symptoms of ADHD in 52 obese children/ adolescents & revealed a significant correlation between TNF-α & hyperactivity/impulsivity [28].

This can be explained by the fact that inflammatory markers have been proved to be one of the key markers linked to impulsive behavior [29]. In addition, many studies have established a correlation between impulsivity and inflammatory processes [30, 31].

In our study, by comparing between subtypes of ADHD, no significant difference was found regarding total, verbal, performance IQ, however, a high statistical significant difference was found in all subscales of Conners' scale.

These findings were similar to that of Oner et al. who evaluated 537 ADHD patients aged between 6-15 and both combined and inattentive subtypes, using WISC, they found that total and performance IQ were not significantly different [32]. Moreover, similarly to our result, they found that Verbal IQ was higher among the inattentive subtype, but also not statistically significant.

Also, in the study of Grizenko et al. ADHD children, Combined/Hyperactive versus Inattentive subtypes were evaluated & no IQ difference was found between both groups[33]. This can be explained by the fact that relation between

Table 3. Comparison between subtypes of ADHD regarding WISC, Conner's test

	Hyperactive /Impulsive (N=16)	Inattentive (N=6)	Combined (N=8)	F test	P value
WISC(mean ± SD)					
Total IQ	97.94 ± 1.81	98.00 ± 1.79	97.38 ± 1.77	0.3	0.73
Verbal IQ	98.00 ± 1.86	98.67 ± 1.03	96.63 ± 2.56	2.1	0.14
Performance IQ	97.44 ± 2.48	98.50 ± 1.87	97.63 ± 2.00	0.48	0.62
Conners' scale					
Cognitive problems	70.69±11.25	78.83 ± 5.98	83.13 ± 6.25	5.17	0.012
Hyperactivity	84.94 ± 7.11	57.50 ± 3.26	81.13 ± 5.73	43.62	<0.0001
Inattention	54.93 ± 1.81	79.50 ± 7.05	77.25 ± 7.04	67.8	<0.0001
Liability	63.69±11.25	53.00 ± 5.37	73.13±12.75	5.91	0.007
Hyperactivity/impulsivity	77.88 ± 5.81	53.55 ± 6.52	76.38±12.31	20.76	<0.0001

Table 4. Correlation between MMP-2, MMP-9 and TNF-α level and various parameters

	MMP-2		MMP-9		TNF-α	
	R	P value	R	P value	R	P value
Age	0.16	> 0.05	0.09	> 0.05	0.397	< 0.001*
IQ	- 0.39	< 0.001*	- 0.48	< 0.001*	- 0.44	< 0.001*
Conners' scale						
Cognitive problems	0.347	< 0.001*	0.41	< 0.001*	0.103	> 0.05
Hyperactivity	0.093	> 0.05	0.031	> 0.05	0.083	> 0.05
Inattention	0.03	> 0.05	0.037	> 0.05	0.43	< 0.001*
Liability	0.053	> 0.05	0.064	> 0.05	0.072	> 0.05
Hyperactivity/impulsivity	0.064	> 0.05	0.076	> 0.05	0.24	< 0.001*

*High significance, P value < 0.001

the cognitive problems and behavioral difficulties in ADHD is bidirectional [34].

In our study, TNF-α level was positively correlated with age, whereas, no correlation was found between MMP-2, MMP-9 and age. Many studies suggest the effect of age on cytokines expressiveness [35]. A study of 37 children aged between 1 and 17 years revealed that TNF-α concentration had a positive association with age [36]. However, similarly to our result, Kadziela-Olech et al. [25] didn't prove any relation between MMP-9 level and age in his study, to the contrary, Bonnema et al. found that MMP-2 and age were related positively whereas a negative relation exists between MMP-9 and age[37]. Our study also revealed a negative correlation between MMP-2, MMP-9, TNF-α level and IQ.

Kudo et al. investigated the relation between MMP 9 and cognitive function and found significant negative relation between MMP 9 levels and verbal, performance and total IQ[38]. Also, Jung et al. investigated the relation between intelligence and cytokines and found a negative association between TNF-α and vocabulary and full-scale scores[39].

A correlation was found between MMP-2, MMP-9 levels and cognitive problems. MMPs have been shown to have a vital role in various pathological as well as physiological processes in the brain particularly those influencing memory and the process of learning. MMP-9 was found to be necessary for hippocampus-dependent learning, as well as amygdala-dependent positive conditioning, interestingly, in human cognition [40].

Also, our study revealed a correlation between TNF-α and inattention, Hyperactivity/ impulsivity.

Recent studies shows the role of TNF-α on the functions of the brain. It was found that the A allele of TNF-α affects cognitive functions [41]. Also, TNF-α have a role in neurodegeneration, high TNF-α is associated with cognitive decline [42].

Moreover, kim et al. found that TNF-α had strong correlation with frontal theta activity reflecting the presence of frontal dysfunction which is related to the impulsive behavior[29]. Also, a recent study was held by Gassen et al. they figured out a correlation between difficulties in making decision as a result of impulsivity and immediate gratification and the release of cytokines including TNF-α. Their results point to the role of the immune system in impulsivity bringing new perspectives to future researchers[43].

CONCLUSION

ADHD is a chronic disorder affecting the developmental process in children. Though, scientific studies have enormously increased, yet, the underlying mechanism of ADHD remains elusive. So far, our study illustrates the co-occurrence of inflammatory process and ADHD, but further studies on larger sample are needed to reach a more definitive conclusion.

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Conflict of interests

The authors declare that they have no conflict of interests.

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