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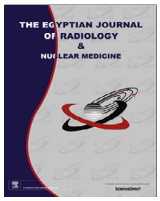

Original Article

# T2*magnetic resonance imaging: A non-invasive biomarker of brain iron content in children with attention-deficit/ hyperactivity disorder

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ABSTRACT

*Purpose:* The aims of this study were the followings: First: To compare brain iron content in children with Attention-Deficit/Hyperactivity Disorder (ADHD) and healthy control subjects, estimated by T2* MRI value and its reciprocal R2*. Second: To assess the association between brain iron content and distinct types of ADHD (predominantly inattentive, predominantly hyperactive/impulsive, or combined). Third: To test the ability of T2* MRI to grade the severity of ADHD.

*Patients and methods:* 35 children (17 ADHD patients and 18 healthy non-ADHD controls) underwent T2*-MRI to assess brain iron content. R2* value is calculated for both thalami.

*Results:* ADHD group showed significantly lower R2* (mean 14.9 $s^{-1}$ ± 1.3) value when compared to control group (mean R2* 16.6 $s^{-1}$ ± 0.9) ($p$ =< 0.001). Best cutoff value for R2* was 15.65 $s^{-1}$, and R2* less than 15.65 $s^{-1}$ showed good AUC for prediction of ADHD. Combined ADHD type showed significantly lower R2* when compared to inattentive type ($p$ = 0.033 respectively). No significant correlations were found between R2* value and severity of ADHD.

*Conclusion:* T2* MRI represents a reliable non-invasive tool for probing brain iron contents. Lower R2* values correlate with ADHD type but not with ADHD severity.



## 1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is considered as one of the most common neuropsychiatric disorders in childhood, with incidence of 5% of school age children [1,2]. It is characterized by age-inappropriate symptoms of inattention, impulsiveness, and hyperactivity [3].

The definite pathophysiology of the symptoms is unclear despite various studies already done. The etiology

*Abbreviations*: ADHD, Attention- Deficit/Hyperactivity Disorder; AUC, area under curve; ROC, receiver operating curve; PPV, positive predictive value; NPV, negative predictive value; ROI, region of interest.

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of ADHD is multifactorial with incorporation of genetic and acquired factors in majority of cases. A primary genetic cause is related to dopamine deficit, but secondary causes such as environmental factors, nutritional and endocrine disorders may also contribute [1,4,5]. Reduced serum and brain iron have been reported in ADHD and suggest that iron metabolism may also be disrupted along with an abnormal dopaminergic system [6–8]. Iron plays an important role in children physical and behavioral well-being [9,10] and supports mental performance by acting as a co-enzyme involved in production and liberation of neurotransmitters. Many researchers have studied the relation between decreased serum iron and ADHD [11–13]. However, serum ferritin is not an accurate biomarker for brain iron content [11,7,14] and correlation of peripheral iron with brain iron content is still unclear. Although low peripheral iron levels may negatively affect brain iron, several authors failed to ascertain an association between peripheral and brain iron [15]. Therefore, research work on iron status in ADHD should not depend on serum ferritin levels.

Several magnetic resonance imaging (MRI) sequences have been introduced for in vivo iron probing and quantification in different organs especially liver, heart and brain [16–20]. Transverse relaxation rate ($T2^*$) value and its reciprocal mathematically calculated $R2^*$ value (inverse of $T2^*$) are promising available techniques to indirectly measure brain iron content [6,21–23].

$T2^*$ relaxation is defined as the decay of transverse magnetization seen with multi echo gradient (GRE) sequences obtained at multiple echo times. $T2^*$ relaxation is one of the principle determinants of image contrast with GRE sequences. Reduced $T2^*$ in iron loaded tissues is attributed to the interaction between high molecular weight iron compounds (e.g. ferritin and hemosiderin) and water molecules [24]. This hypothesis relies on the fact that random motion of water molecules causes irreversible decay of signal with subsequent T2 shortening. Since iron levels differ in specific brain areas in plenty of neurological diseases, this interaction may provide a method for monitoring iron content [16]. However, $R2^*$ methods proved to be more sensitive to decreased iron level within the tissue [21].

The aims of this study were the following: First: To compare brain iron content in children with ADHD and healthy control children, estimated by $T2^*$ MRI value and its reciprocal $R2^*$. Second: To assess the association between brain iron content and distinct types of ADHD. Third: To test the ability of $T2^*$ MRI to grade the severity of ADHD.

## 2. Subjects and methods

This prospective comparative case-control study was conducted from December 2014 to December 2015. Twenty children with newly diagnosed drug naive ADHD were enrolled consecutively during their initial presentation at Pediatric Behavior Outpatient Clinic, Neurology unit, University Children Hospital. Patients' ages ranged between 6 and 15 years. In addition, eighteen age and sex matched healthy children were recruited from patient's relatives, during the same period to participate as a control group. Exclusion criteria of ADHD group were as follows: intellectual deficiency (IQ < 79), current or past iron supplementation for a year preceding examination, anemia, chronic disease affecting iron metabolism, and comorbid neuropsychiatric disorders other than ADHD. Exclusion criteria of control group were as follows: intellectual deficiency (IQ < 79), current or past iron supplementation for a year preceding examination, anemia, chronic disease affecting iron metabolism, any psychiatric (as per DSM-IV-TR criteria) or neurological disorders.

ADHD diagnosis was done by clinical examination and by using the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders, text revision (DSM-IV-TR) criteria [3]. All participants were interviewed with KID-SCID externalizing disorder modules to confirm assessment psychiatric disorders [25].

The diagnosis and severity of ADHD were further promoted by using the cognitive, hyperactivity, and ADHD indices of the validated Arabic version of Conner's Parent Rating Scale-Revised (CPRS-R) [26] completed by both parent and teachers of participant children. Patients were categorized according to the subtype of ADHD into combined type and predominantly inattentive type and according to severity of ADHD into mild, moderate, and severe.

Comprehensive physical and neurological examinations were accomplished by a trained pediatric neurologist with particular attention to signs of iron deficiency anemia. A complete blood count was obtained for all participants. A validated Arabic translated version of the Stanford Binet-V [27] was used to assess the IQ of patients and controls.

Written informed consent was obtained from parents of included patients and controls before participation in the study. The protocol of the study was approved by the Institutional Research Board (IRB) of Mansoura Faculty of Medicine.

### 2.1. MRI imaging protocol

All participants received MR imaging using 1.5 T MR Unit (Ingenia; Philips Medical system, Best, Netherlands) with head coil in the supine position with the head first. No anesthesia was used. Examination was done on the base of transverse relaxation rates ($T2^*$ or its inverse $R2^*$). $T2^*$ MRI: a multi-slice multi-echo gradient sequence to provide multiple echoes and multiple slices. The sequence parameters were as follows: TR120 ms, TE 1.00 ms, and multiple TEs at 1 ms, 1.8 ms, 2.6 ms, 3.5 ms, 4.3 ms, 5.1 ms, 5.9 ms, 6.8 ms, 7.6 ms, 8.4 ms, 9.2 ms and 10.1 ms (i.e. 12 TEs equally spaced at 0.8 ms), field of view 28 cm, matrix acquisition: 164/136; number of axial slices: 9; slice thickness: 10 mm; acquisition time: 3 min.

### 2.2. Image analysis

Selection of appropriate axial image was first done at the level of basal ganglia and thalami. Region of interest (ROI) is drawn on right thalamus to derive the $T2^*$ signal intensity decay curve and table and another ROI of similar diameter is drawn in left thalamus (Fig. 1). Fixed ROI was

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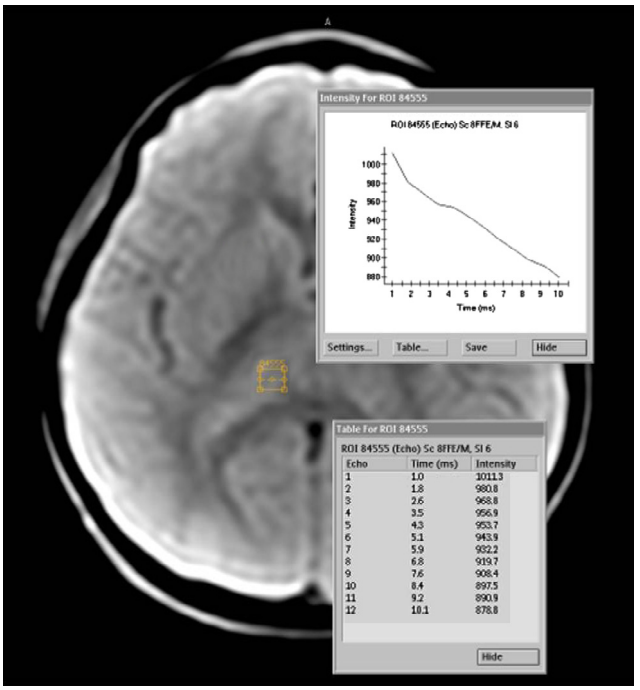


**Fig. 1.** Axial MRI image at the level of basal ganglia and thalami. Region of interest (ROI) is drawn on right thalamus to derive the T2* signal intensity decay curve.

used in all MRI examinations. T2* signal intensity decay curve and table were displayed on the image. T2* decay is calculated according to the following equation: $I_t = I_{t=0} X\, e^{-t/T2*}$ [28].

The signal intensity ($I$) at time ($t$) equals the intensity at time zero multiplied with the exponential component that describes the decay ($e$ exp $-t/T2^*$). Data of T2* signal intensity curve were transferred to Microsoft excel sheet and were used to calculate the T2* value according to the equation: $T2^* = -\Delta TE/\ln [I_{TE2}/I_{TE1}]$ [28].

The T2* value (in m.s) is the time between the two echoes (delta TE's) divided by the natural logarithm of the division of signal intensity at TE2 by the intensity at TE1. Mean T2* value was calculated for right thalamus and then left thalamus. R2* value which is the reciprocal of T2*(1/T2*) was derived for both thalami. The left- and right-sided thalami were averaged to produce a single T2* and R2* value for each participant to simplify calculations. The average R2* value was used in statistical analysis.

### 2.3. Statistical analysis

The statistical analysis of data was done using Excel program (Microsoft Office 2013) and IBM SPSS (statistical package for social science) program (SPSS, Inc, Chicago, IL) version 21:

- Qualitative data were presented as frequency and percentage.
- Quantitative data were presented by mean, SD.
- Chi square test was used to compare groups.
- Comparisons between two groups were done using *t*-test in normal data distribution.
- Diagnostic performance was determined by constructing a "receiver-operating characteristic" (ROC) curve and calculating the area under the ROC (AUROC) curve. From these curves, sensitivities, specificities and the best cutoff values were established, which were the values that maximized the sum of the sensitivity and specificity to identify patient status. Diagnostic validity was estimated using sensitivity, specificity, positive (PPV) and negative (NPV) predictive values.
- *P* is significant if <0.05 at confidence interval 95%.

## 3. Results

### 3.1. Demographics

This study included 20 children with ADHD; however, 3 of them were excluded due to motion artifact in 2 cases and susceptibility artifact in one, so the final ADHD group included 17 patients. Age range in ADHD group was 6–15, mean 8.38 ± 1.8 and there were 12 males and 5 females. The seventeen patients were categorized according to the subtype of ADHD into inattentive subtype ($n$ = 7, 41.2%), and combined type ($n$ = 10, 58.8%) and according to severity of ADHD into mild ($n$ = 1, 5.8%), moderate ($n$ = 8, 47.1%), and severe ($n$ = 8, 47.1%).

Eighteen healthy children were enrolled in control group, and their age range was 6–15, mean age 8.5 ± 1.7; there were 11 males and 7 females. ADHD group and control group did not significantly differ with regard to age and sex distribution (Table 1).

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**Table 1**
Demographic characteristics of studied groups.

| | Control | | ADHD | | *p* |
|---|---|---|---|---|---|
| | *N* = 18 | | *N* = 17 | | |
| Age (years); mean, SD | 8.50 | 1.689 | 8.38 | 1.781 | 0.842 |
| Males; *N*, % | 11 | 61.1% | 12 | 70.6% | 0.555 |
| Females; *N*, % | 7 | 38.9% | 5 | 29.4% | |
| *Types of ADHD* | | | | | |
| Inattentive | | | 7 | 41.2% | |
| Combined | | | 10 | 58.8% | |
| *Severity of ADHD* | | | | | |
| Mild | | | 1 | 5.8% | |
| Moderate | | | 8 | 47.1% | |
| Severe | | | 8 | 47.1% | |

Data are expressed as mean ± SD.
ADHD: Attention-Deficit/Hyperactivity Disorder.
Age: *t*-test, gender: chi square test.

### 3.2. Brain iron content

The mean R2* value was 14.9 $s^{-1}$ ± 1.3 in ADHD group and 16.6 $s^{-1}$ ± 0.9 in healthy control group. ADHD group showed significantly lower R2* value when compared to control group ($p$ =< 0.001) (Table 2, Fig. 2).

ROC of R2* values was constructed for discrimination between ADHD and control groups. Best cutoff value for R2* was 15.65 $s^{-1}$ (at 95% CI). R2* less than 15.65 $s^{-1}$ showed good AUC for prediction of ADHD cases. Other performance characteristics are 70.6% sensitivity, 94.4% specificity, 92.3% PPV, 77.3% NPV and 82.9% accuracy (Table 3, Fig. 3).

According to ADHD subtypes, combined type showed significantly lower R2* when compared to inattentive type (Table 4). No significant differences were found in R2* values according to severity (Table 5).

**Table 2**
Studied groups comparison: thalamic R2* value.

| | Control *N* = 18 | | ADHD *N* = 17 | | *p* |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| R2* ($s^{-1}$) | 16.594 | 0.9117 | 14.9 | 1.3426 | <0.001 |

*t*-test.
* *P* value < 0.05 is significant.

## 4. Discussion

We found that thalamic R2* value is significantly lower in ADHD group than control group. Thalamus has been chosen for placement of ROI because it is considered one of the regions of highest iron and dopamine concentrations in the brain [29–31]. While neuroimaging studies of ADHD have not generally focused specifically on thalamic nuclei, thalamic abnormalities have been noted with increasing frequency with a range of neuroimaging techniques [32,33].

A crucial relationship between brain iron and the dopaminergic system has been broadly illustrated. Changes in brain iron and/or dopaminergic functional units are associated with alterations in motivation, attention, working memory, and motor control [34–36].

These results are in agreement with the work done by Cortese et al. [6] who associated reduced thalamic brain iron, with the "hypoarousal" theory of ADHD because the thalamus is involved in cortical arousal via thalamocortical connections; meanwhile, our results are considered more accurate due to the use of 1.5 T MRI scanner that lessened the effect of local field inhomogeneities gained in the 3 T scanners. However, Adisetiyo et al. [37] found no significant difference between R2* measurements in ADHD group and control group.

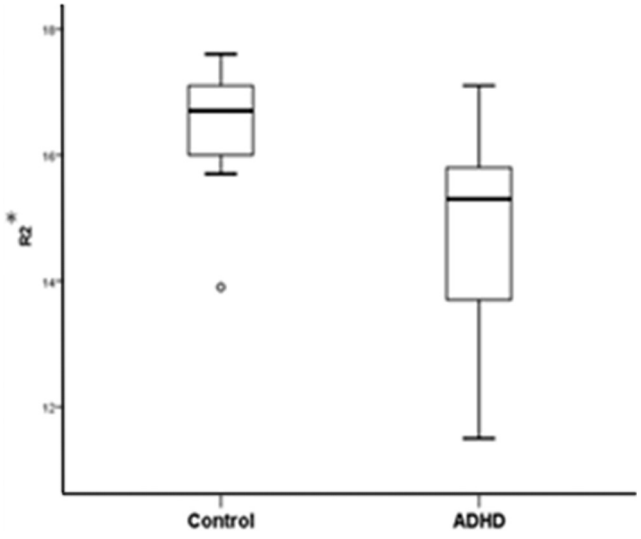


**Fig. 2.** Box plots demonstrates R2* values in studied groups. The mean R2* value was 14.9 $s^{-1}$ ± 1.3 in ADHD group and 16.6 $s^{-1}$ ± 0.9 in healthy control group.

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**Table 3**
AUC and performance characteristics of R2* values for discrimination between ADHD and control groups.

| | AUC | p | 95% CI | | Cutoff | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| R2* | 0.863 | <0.001 | 0.740 | 0.986 | <15.65 | 70.6 | 94.4 | 92.3 | 77.3 | 82.9 |

AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

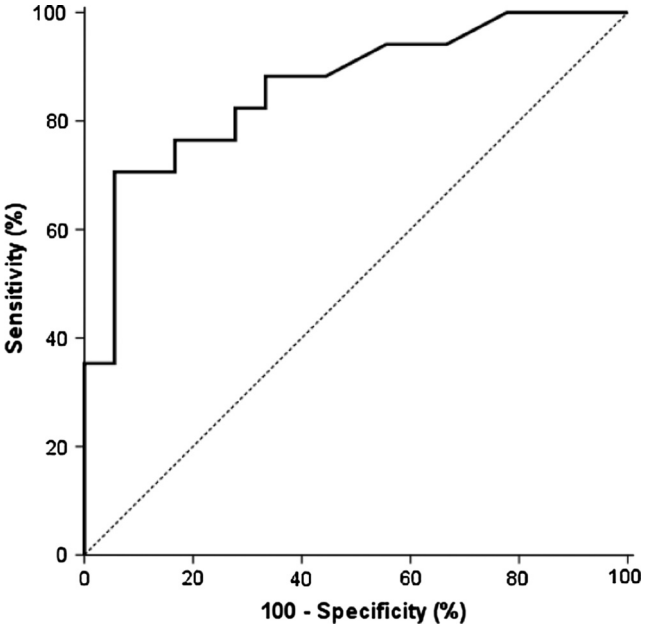


**Fig. 3.** ROC curve of R2* for discrimination between ADHD and control groups. Performance characteristics are 70.6% sensitivity, 94.4% specificity.

**Table 4**
Comparison of ADHD subtypes: thalamic R2* value.

| | Inattentive ADHD N = 7 | | Combined ADHD N = 10 | | p |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| R2* ($s^{-1}$) | 15.714 | 0.6962 | 14.140 | 1.6608 | 0.033 |

*t*-test.
* *P* value < 0.05 is significant.

**Table 5**
Comparison of ADHD severity: thalamic R2* value.

| | Mild to moderate N = 9 | | Severe N = 8 | | p |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| R2* ($s^{-1}$) | 14.811 | 1.6796 | 14.763 | 1.4813 | 0.951 |

*t*-test.
* *P* value < 0.05 is significant.

The present study revealed that combined ADHD type showed significantly lower R2* values than inattentive type. Significant association present with combined type doesn't mean that ADHD children would not have worse cognitive performance but rather have combined cognitive and behavioral problems. If there is a differential association between brain iron levels and both ADHD symptom factors, as suggested by our study, it is unclear whether biological factors underlie it or whether it is rather due to a differential sensitivity of the rating scales used to catch these symptom factors.

Previous studies implied that low serum ferritin had a tendency to be firmly connected with the hyperactivity subtype of ADHD [13,38] but no one did this association with brain iron levels. Our study suggests that brain iron stores may be more essential in combined symptom type than predominantly inattentive type. Therefore, it can be contemplated that the effects of iron substitution treatment might be differential in these domains. Thus, assessment of baseline brain iron levels with R2* imaging may provide an alternative noninvasive diagnostic biomarker for ADHD subtypes.

Our results showed that disease severity didn't correlate with R2* values. Some studies revealed a significant inverse correlation between severity of ADHD symptoms and serum ferritin levels [13,38–40], while others failed to replicate this relationship [11,14]. To date, no studies were done to correlate ADHD severity with brain iron levels.

To our knowledge, this is the primary study that evaluated the association between estimated brain iron levels and disease severity and the distinct subtypes of ADHD. It is also the first study to reach a cutoff value for R2* as an attempt to utilize this MRI technique to discriminate between ADHD patients and healthy subjects. R2* value

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of 16 could be used as a cutoff value to discriminate between ADHD and healthy subjects with 0.86 area under curve, 70.6% sensitivity, 94.4% specificity, 92.3% PPV, 77.3% NPV and 82.9% accuracy.

### 4.1. Study limitations

First, small number of patients was included in the study and small number of patients in ADHD subgroups. Second, lack of association study was between brain iron and serum iron and ferritin levels. Third, software for T2* and R2* values was not built in the MRI workstation.

### 4.2. Recommendations

Larger longitudinal studies are needed to validate our preliminary findings. However, our R2* measurements may be utilized as an empirical reference for the quantification of iron content in thalami of ADHD patients using MR imaging at 1.5 T.

## 5. Conclusion

T2* MRI represents a reliable non-invasive tool for probing brain iron contents and that lower R2* values correlate with ADHD type but not with disease severity.

## Ethical standards and patient consent

We declare that all human studies have been approved by the institutional Review board of Faculty of Medicine, Mansoura University (MFM-IRB) (Code Number of final proof: R/16.03.99) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave written informed consent from parents of enrolled patients and control group prior to inclusion in this study.

## Experimental studies

We declare that this manuscript does not contain experimental or animal studies.

## Author contributions

1 Guarantor of integrity of the entire study: Bothina Hasaneen
2 Study concepts: Bothina Hasaneen, Sarhan MM
3 Study design: Bothina Hasaneen, Sarhan MM, Ashamallah G.A
4 Definition of intellectual content: Bothina Hasaneen
5 Literature research: Samir S, Sakarana A
6 Clinical studies: Bothina Hasaneen, Sarhan MM, El-Sabbagh EM, EL Assmy M
7 Experimental studies: No experimental studies in this article.
8 Data acquisition: Bothina Hasaneen, Ashamallah G. A, Sakarana A.
9 Data analysis: Bothina Hasaneen, Samir S., Ashamallah G.A
10 Statistical analysis: Iman Fawzy
11 Manuscript preparation: Bothina Hasaneen, Ashamallah G.A
12 Manuscript editing: Sakarana A, [1]Ashamallah G.A
13 Manuscript review: Bothina Hasaneen, Samir S, Sarhan MM, ELAssmy M, Sakarana A, Ashamallah G.A.

## Conflict of interest

Authors declare no conflict of interest.

## Acknowledgments

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## References

[1] Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry 2007;164(6):942–8.
[2] Biederman J. Attention-deficit/hyperactivity disorder: a selective overview. Biol Psychiatry 2005;57(11):1215–20.
[3] American psychiatric association: diagnostic and statistical manual of mental disorders. 4th ed., (DSM-IV). Washington, DC, APA; 1994.
[4] Millichap JG. Etiologic classification of attention-deficit/hyperactivity disorder. Pediatrics 2008;121(2):e358–65. 28.
[5] Fusar-Poli P, Rubia K, Rossi G, Sartori G, Balottin U. Striatal dopamine transporter alterations in ADHD: pathophysiology or adaptation to psychostimulants? a meta-analysis. Am J Psychiatry 2012;169(3):264–72.
[6] Cortese S, Azoulay R, Castellanos FX, Chalard F, Lecendreux M, Chechin D, et al. Brain iron levels in attention-deficit/hyperactivity disorder: a pilot MRI study. World J Biol Psychiatry 2012;13(3):223–31.
[7] Cortese S, Angriman M, Lecendreux M, Konofal E. Iron and attention deficit/hyperactivity disorder: what is the empirical evidence so far? a systematic review of the literature. Expert Rev Neurother 2012;12(10):1227–40.
[8] Mohamed WMY, Unger EL, Kambhampati SK, Jones BC. Methylphenidate improves cognitive deficits produced by infantile iron deficiency in rats. Behav Brain Res 2011;216(1):146–52.
[9] Liu J, Hanlon A, Ma C, Zhao S, Cao S, Compher C. Low blood zinc, iron, and other sociodemographic factors associated with behavior problems in preschoolers. Nutrients 2014;6(2):530–45. 27.
[10] Liu J, Raine A. The effect of childhood malnutrition on externalizing behavior. Curr Opin Pediatr 2006;18(5):565–70.
[11] Menegassi M, de Mello ED, Guimarães LR, Matte BC, Driemeier F, Pedroso GL, et al. Food intake and serum levels of iron in children and adolescents with attention-deficit/hyperactivity disorder. Rev Bras Psiquiatr 2010;32(2):132–8.
[12] Konofal E, Cortese S, Lecendreux M, Arnulf I, Mouren MC. Effectiveness of iron supplementation in a young child with attention-deficit/hyperactivity disorder. Pediatrics 2005;116(5):e732–4.
[13] Konofal E, Lecendreux M, Arnulf I, Mouren MC. Iron deficiency in children with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 2004;158:1113–5.
[14] Millichap JG, Yee MM, Davidson SI. Serum ferritin in children with attention-deficit hyperactivity disorder. Pediatr Neurol 2006;34(3):200–3.
[15] Godau J, Klose U, Di Santo A, Schweitzer K, Berg D. Multiregional brain iron deficiency in restless legs syndrome. Mov Disord 2008;23(8):1184–7.
[16] Drayer B, Burger P, Darwin R, Riederer S, Herfkens R, Johnson GA. MRI of brain iron. Am J Roentgenol 1986;147(1):103–10.
[17] Carpenter J-P, He T, Kirk P, Roughton M, Anderson LJ, de Noronha SV, et al. On T2∗ magnetic resonance and cardiac iron. Circulation 2011;123(14):1519–28. 12.

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[18] Gandon Y, Olivie D, Guyader D, Aube C, Oberti F, Sebille V, et al. Non-invasive assessment of hepatic iron stores by MRI. The Lancet 2004;363(9406):357–62.
[19] Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, Bunce NH, et al. Cardiovascular T 2-star(T 2∗) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J 2001;22 (23):2171–9.
[20] Wood JC, Tyszka JM, Carson S, Nelson MD, Coates TD. Myocardial iron loading in transfusion-dependent thalassemia and sickle cell disease. Blood 2004;103(5):1934–6.
[21] Ordidge RJ, Gorell JM, Deniau JC, Knight RA, Helpern JA. Assessment of relative brain iron concentrations using T2-weighted and T2∗-weighted MRI at 3 Tesla. Magn Reson Med 1994;32(3):335–41.
[22] Miszkiel KA, Paley MNJ, Wilkinson ID, Hall-Craggs MA, Ordidge R, Kendall BE, et al. The measurement of R 2, R2∗ and R 2′ in HIV-infected patients using the prime sequence as a measure of brain iron deposition. Magn Reson Imaging 1997;15(10):1113–9.
[23] Siemonsen S, Finsterbusch J, Matschke J, Lorenzen A, Ding X-Q, Fiehler J. Age-dependent normal values of T2∗ and T2' in brain parenchyma. Am J Neuroradiol 2008;29(5):950–5.
[24] Gossuin Y, Muller RN, Gillis P. Relaxation induced by ferritin: a better understanding for an improved MRI iron quantification. NMR Biomed 2004;17(7):427–32.
[25] Smith DC, Huber DL, Hall JA. Psychometric evaluation of the structured clinical interview for DSM-IV childhood diagnoses (KID-SCID). J Hum Behav Soc Environ 2005;11(3–4):1–21.
[26] El -Behery DA Conner's Scales. Egyptian Anglo Library (2011).
[27] Safwat Farag. Arabic version of stanford binet intelligence scales, 5th ed., Egypt; 2007.
[28] Springorum, rudolf. T2* (T2 star) calculation of the myocardium. Available from: <http://clinical.netforum.healthcare.philips.com/us_en/Operate/Application-Tips/MRI/T2-(T2-star)-calculation-of-the-myocardium.accessed> at 29/6/2016.
[29] Hallgren B, Sourander P. The effect of age on the non-haemin iron in the human brain. J Neurochem 1958;3:41–51.
[30] Beard JL, Connor JR. Iron status and neural functioning. Annu Rev Nutr 2003;23:41–58.
[31] Khalil M, Enzinger C, Langkammer C, Tscherner M, Wallner-Blazek M, Jehna M, et al. Quantitative assessment of brain iron by R2∗ relaxometry in patients with clinically isolated syndrome and relapsing–remitting multiple sclerosis. Mult Scler 2009;15 (9):1048–54.
[32] Arcos-Burgos M, Jain M, Acosta MT, Shively S, Stanescu H, Wallis D, et al. A common variant of the latrophilin 3 gene, LPHN3, confers susceptibility to ADHD and predicts effectiveness of stimulant medication. Mol Psychiatry 2010;15(11):1053–66.
[33] Ivanov I, Bansal R, Hao X, Zhu H, Kellendonk C, Miller L, et al. Morphological abnormalities of the thalamus in youths with attention deficit hyperactivity disorder. Am J Psychiatry 2010;167 (4):397–408.
[34] McCann JC, Ames BN. An overview of evidence for a causal relation between iron deficiency during development and deficits in cognitive or behavioral function. Am J Clin Nutr 2007;85(4):931–45.
[35] Lozoff B. Early iron deficiency has brain and behavior effects consistent with dopaminergic dysfunction. J Nutr 2011;141 (4):740S–6S.
[36] Egerton A, Mehta MA, Montgomery AJ, Lappin JM, Howes OD, Reeves SJ, et al. The dopaminergic basis of human behaviors: a review of molecular imaging studies. Neurosci Biobehav Rev 2009;33 (7):1109–32.
[37] Adisetiyo V, Jensen JH, Tabesh A, Deardorff RL, Fieremans E, Di Martino A, et al. Multimodal MR imaging of brain iron in attention deficit hyperactivity disorder: a noninvasive biomarker that responds to psychostimulant treatment? Radiology 2014;272 (2):524–32.
[38] Oner O, Alkar OY, Oner P. Relation of ferritin levels with symptom ratings and cognitive performance in children with attention deficit–hyperactivity disorder. Pediatr Int 2008;50(1):40–4.
[39] Juneja M, Jain R, Singh V, Mallika V. Iron deficiency in Indian children with attention deficit hyperactivity disorder. Indian Pediatr 2010;47 (11):955–8.
[40] Cortese S, Faraone SV, Konofal E, Lecendreux M. Sleep in children with attention-deficit/hyperactivity disorder: meta-analysis of subjective and objective studies. J Am Acad Child Adolesc Psychiatry 2009;48(9):894–908.

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